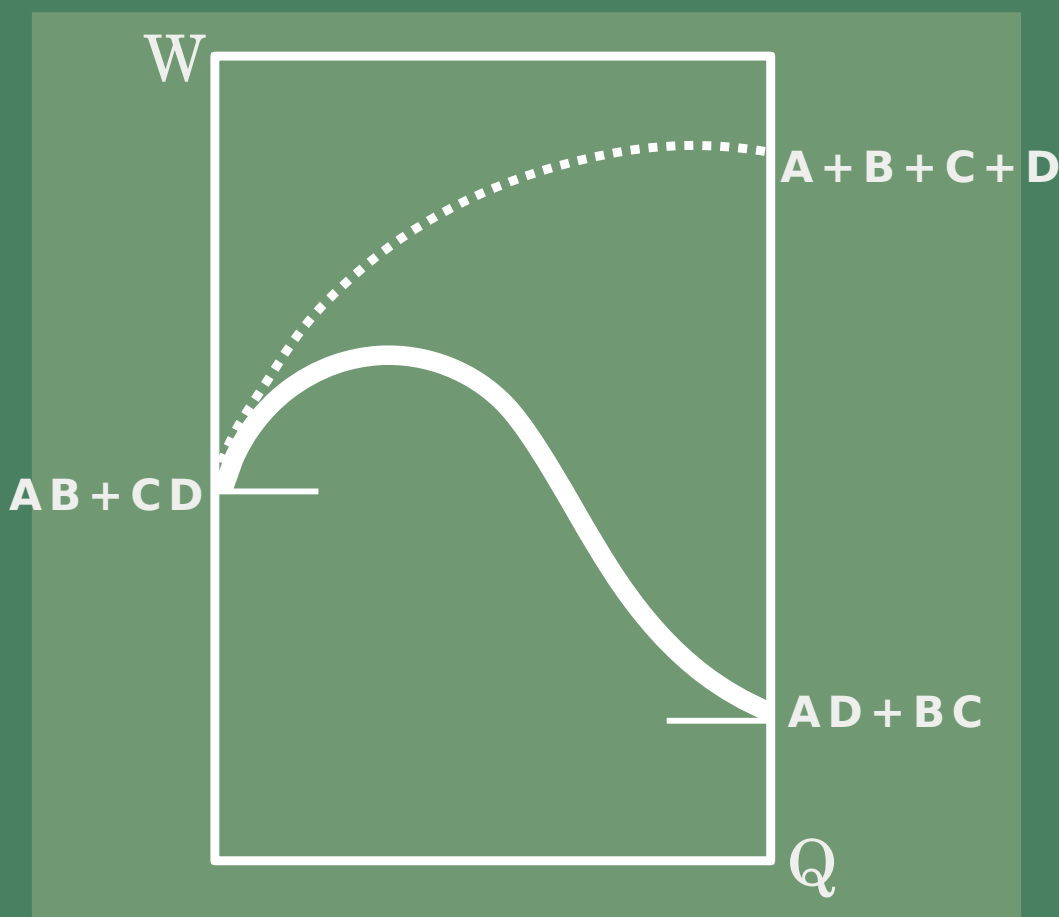


V. A. Afanasiev  
G. E. Zaikov

# In the Realm of Catalysis



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**В. А. Афанасьев, Г. Е. Заиков**

**КАТАЛИЗ  
В ХИМИЧЕСКИХ РЕАКЦИЯХ**

**ИЗДАТЕЛЬСТВО «ЗНАНИЕ»**

**V. A. Afanasiev  
and G. E. Zaikov**

**In the Realm of  
Catalysis**

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# Contents

Introduction	7
Chapter One. An Interview on Catalysis	9
Chapter Two. A Few Words About Industrial Catalysis	15
Chapter Three. Rate of Reaction	21
Chapter Four. Energy Barrier	29
Chapter Five. The Law of Conservation of Disorder	32
Chapter Six. Overcoming the Energy Barrier	38
Chapter Seven. What Next?	42
Chapter Eight. Model Reactions	46
Chapter Nine. The Smile of Mona Lisa	51
Chapter Ten. Acid Catalysis	55
Chapter Eleven. 'Tender Points' of Molecules	65
Chapter Twelve. The Least. What Is It?	71
Chapter Thirteen. Homogeneous Catalysis	78
Chapter Fourteen. Heterogeneous Catalysis	84
Chapter Fifteen. Reaction Medium Acts Like a Catalyst	88
Chapter Sixteen. Catalysis in Biology	95
Chapter Seventeen. Catalysis in the Realm of Elementary Particles	111





## Introduction

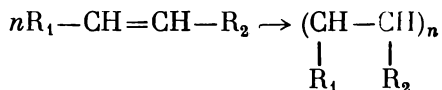
The phenomenon of changing the rate of a chemical reaction by the action of substances that do not alter their own chemical composition during this reaction is called *catalysis*.

The rate of a process is an extremely important factor that determines the efficiency of chemical equipment. Hence one of the basic problems that chemistry faces in the conditions of the scientific and technical revolution is the search for new ways to accelerate chemical reactions. Another vital problem of modern chemistry, which is caused by the ever increasing growth of the chemical industry, is the improvement of the selectivity of chemical processes in which the initial substances are converted into products and in which the amounts of wastes are reduced. It is these wastes which are particularly important with respect to environmental protection and reasonable utilization of natural resources, which are, unfortunately, not unlimited.

These goals can only be attained through efficient means, and these are, first and foremost, catalysts. But the search for suitable catalysts is another problem to be solved.

In the past, and even in the recent past, many highly effective catalysts were discovered accidentally, among substances that had not been regarded as potential catalysts, and sometimes by persons who never intended to find any catalysts.

Thus, quite unexpectedly, the catalysts for the Ziegler stereospecific polymerization



were discovered. As it happened, the reaction was carried out in a kettle that had not been washed out from residual

quantities of the products of the previous reaction. The result of this "negligence", and also of the thoughtful attentiveness of the investigators, who did not fail to note the unexpected effect, was the lucky discovery of a new catalyst that gave a great impetus to the development of the polymer science and technology.

This story is however not a perfect example, and it would be contrary to scientific principles to arbitrarily try all substances at hand for their possible catalytic properties. A discovery, if any occurs, will then simply be accidental, and a true investigator can never rely upon it. A 'lucky' accident will come by accident, whereas the present and future of catalysis depends upon a strictly scientific and quantitative approach to the problem, a detailed study of the mechanism of chemical reactions, and on a scientifically motivated search for new catalysts.

In this popular narrative we have attempted to unveil some 'secrets' of catalytic reactions and to provide illustrations which are more closely related to our own field of research. We have placed special emphasis on the kinetic principles of catalysis. In the discussion of catalysis we considered it necessary to give the reader the basic principles of the theory of chemical catalysis and gave examples of catalysis in biology and in industry. It was not our aim to discuss all aspects of catalysis in chemistry and biology, and in this respect this book is far from being comprehensive. The authors will therefore gladly accept all constructive criticism from our readers. And finally we should like to express our gratitude to Marina Artsis who helped us prepare this manuscript.

## Chapter One

### An Interview on Catalysis

"We got used to listen to the stories, full of miracle and secrecy, the action of which takes place in far distance or in ancient times. There exists another kingdom full of miracle and secrecy—this is the inner world of ordinary things, that surround us, if we only be able to peep into it.... The beauty of this microworld cannot be compared with the charm of magic stories, because it is genuine beauty."

*Donald J. Hughes, 1950*

In the process of their investigation of the surrounding world, scientists have established a kind of hierarchy in the micro-world levels. The world that we are going to discuss in this book is the realm of molecules, whose mutual conversions make out the subject matter of chemistry. We shall not deal with the entire subject of chemistry, but only touch on its component part concerning the dynamics of changes in the chemical structure of molecules. It is a commonplace that molecules consist of atoms, and the latter of the nuclei and electron shells enveloping them, that the properties of molecules depend on the nature of the component atoms and the order in which they are arranged with respect to one another, that chemical and physical properties of substances depend on the properties of molecules and the nature of their interconnections. Since it is assumed that the reader is aware of these general concepts, we shall dwell on the problems connected with the rate of chemical reactions. The process in which molecules convert into one another can proceed at different rates. This rate can be altered by heating or cooling the mixture of the reacting molecules. The reaction rate is as a rule accelerated by heating, but this is not the only means to accelerate chemical conversions. There is another, more effective method, known as catalysis, which is now widely used in the manufacture of many products.

The first scientific ideas of catalysis arose together with the development of the atomic theory of structure of material substance. In 1804, i.e. in a year after Dalton, one of the creators of the modern atomistic theory, had formulated the law of multiple proportions, Clement and Desormes reported detailed data on the acceleration of oxidation of sulphur dioxide gas in the presence of nitrogen oxides during manufacture of sulphuric acid by the chamber method. Six years later, Kirchhoff reported his observations concerning the accelerating action of dilute mineral acids on hydrolysis of starch to glucose. These two observations opened a new era of experimental studies of the chemical phenomenon that was entirely new for that time and to which Berzelius (Sweden) gave, in 1835, the name of 'catalysis' (from Greek *katalysis*, dissolution).

This, in short, is the history of discovery of catalysis, which can justly be considered one of the fundamental natural phenomena.

We shall now consider modern definitions of catalysis that are commonly used by scientists and then classify catalytic processes, since it is with a general classification that any exact science begins.

Following Bergman, who said that physics is what physicists study, and extending this definition to chemistry, we can also say that catalysis is what physicists and chemists study. But this figurative definition cannot of course describe such a complicate phenomenon, and beginning with Berzelius, many scientists attempted to define catalysis. In our opinion the best definition belongs to the Soviet scientist G. K. Boreskov who said that "from the phenomenological point of view, catalysis can be defined as the excitation of chemical reactions, or changing of their rates, by the action of substances, catalysts, which participate repeatedly in intermediate chemical interactions with the reactants, and which are regenerated into their starting chemical composition after each intermediate cycle".

The most surprising in this definition is that the substance accelerating the chemical process is not spent in the reaction. Whenever we want to accelerate the motion of a heavy body, we push it, and hence spend energy. The higher the amount of spent energy, the higher does the velocity of the moving body become. In an ideal case the amount of spent energy will accurately be equal to the kinetic energy

acquired by a moving body. This is the illustration of the fundamental law of nature, the law of the conservation of energy. From our school days we know that "all changes occurring in nature can be described as this: whatever quantity of anything is taken from a body, the same quantity will be added to another body" (from Lomonosov's letter to L. Euler, 1756).

The question arises, *what* actually and in *what form* is 'taken from' the catalyst and 'added' to a chemical reaction? Is it heat in the form of oscillations of atoms or the chemical energy that could be transmitted, for instance, by the intermediate chemical interaction of the catalyst atoms with the atoms of the reacting molecules? Or do we encounter here with some mysterious force that is unknown to science? Or maybe the problem is senseless on the whole when we deal with catalysis? No, the problem is quite meaningful since no exact science can exist if it starts with the denial of the law of conservation. Hence the question must be answered. And the answer to this question underwent changes along with the development of science. It is interesting to follow these changes in the description of catalysis given by scientists of different generations. Let us begin with the one who was the first to utter the word "catalysis".

J. Berzelius (1837):

"Certain substances contact other substances to produce an effect on them that consists in the generation of a chemical reaction, as a result of which some substances are decomposed and new products are formed without any participation (in these interconversions) of the substance whose presence induces these interconversions. We give the name of catalytic force to the cause that induces this phenomenon."

J. Liebig (1839):

"The assumption that a new force exists is harmful to the progress of science since it probably satisfies the human spirit and thus retards further search.... The catalytic agent, being an inorganic substance or an enzyme, is unstable ...; in the process of decomposition, this agent makes the substances (that otherwise do not react with each other) undergo chemical changes."

M. Faraday (1834):

"Catalytic phenomena can be explained by the known properties of matter without ascribing to it any new faculties."

E. Houdry (1957):

"My life experience suggested my agreement with Liebig theory.... In a few years Liebig renounced his theory, and perhaps he was wrong."

M. Stohmann (1895):

"Catalysis is the movement of atoms in molecules of labile bodies that occurs under the influence of a force originated from some other bodies, and that results in the loss of energy and formation of stable bodies."

W. Ostwald (1895):

"The concept of 'the movement of atoms in molecules' is only hypothetic and cannot therefore be used to define the concept of catalysis.... A catalyst is a substance that, being absent in the products of chemical reactions, changes their rates."

F. Raschig (1906):

"Catalysis is the change in structure of molecules, produced by external causes, that involves the change in chemical properties."

L. Gurvich (1916):

"Catalyzing bodies attract moving molecules much stronger than bodies devoid of catalytic action, and thus they increase the force of impact of molecules that collide with their surfaces."

P. Sabatier (1897):

"As to me, the explanation of catalysis based on unstable or short-lived compounds was like the light of a beacon in all my work in the field of catalysis. It is quite possible that in future this light will fade since the field of science, cultivated thoroughly by our chemical knowledge, will be illuminated by a more powerful lighthouse, of which we have no slightest idea now."

E. Houdry (1957):

"Sabatier compares his theory with a torch of a lighthouse that can fade in the light of recent theories. In my opinion his torch is still alive."

N. I. Kobozev (1957):

"Catalysis is the method of realization of elementary acts without formation of free valencies that, as the bonds break down, are closed immediately on the active centre to form new adsorption bonds; this is the principle of saving free valencies. Omission of formation of free valencies from the elementary acts sharply decreases endothermic properties of such processes to reduce the energy of activation.... There exists a special mechanism of catalytic activation which has not so far been discovered in the known theories of catalysis. And until this mechanism is not discovered and reproduced, a blank space will remain in the field of catalysis."

G. K. Boreskov (1968):

"Catalysis was once regarded as something slightly mysterious, having its specific laws, the discovery of which would suddenly solve the problem of selection. We know that it is not so. Catalysis is a chemical phenomenon in its essence. The change in the reaction rate caused by catalytic action is due to the intermediate chemical interaction of the reactants with the catalyst."

If we put aside the unsuccessful attempt of Berzelius to connect the observed phenomena with the action of an unknown 'catalytic force' then we can conclude from what we have read above that the discussion hovered mainly round physical and chemical aspects of catalysis. The energetic theory of catalysis had been especially popular for a long time. It attempted to bind the process of molecule excitation with the resonance migration of energy.

This theory was backed, for instance, by the following observation. "Nitrogen iodide", Stohmann wrote in 1895, "placed on bass strings of an instrument does not explode when we play with a bow, but it explodes immediately when placed on treble strings. Thus, vibration of atoms produces similar vibration in atoms of other bodies whose molecules fall out; a similar picture is observed with enzymes and fermented bodies.... All these bodies (enzymes) must produce vibration having certain definite height of the tone to destroy labile molecules."

Nobody doubts now that catalysis can be explained on the basis of purely chemical principles. A catalyst interacts with the reacting molecules to form unstable intermediate

compounds which fall out to give the reaction product and the unchanged catalyst. Our modern knowledge of catalysis is best of all expressed by Boreskov.

A question however arises here: if a catalyst takes part in the reaction, can it not give a new equilibrium state? If it were so, the idea of chemical participation of a catalyst in the reaction would contradict the law of the conservation of energy. To avoid this disagreement, scientists had to admit (and later they proved it experimentally) that a catalyst accelerates the reaction in both forward and backward direction. But compounds changing both the rate and the equilibrium of a reaction cannot be considered catalysts in the strict sense of the word.

We have only to add that chemical reactions are as a rule accelerated in the presence of catalysts and such a phenomenon is known as positive catalysis to distinguish from negative catalysis, in which the reaction is hindered by adding a catalyst into the reacting system. Strictly speaking, catalysis always accelerates the reaction rate, but sometimes the acceleration of one stage (for instance, giving a new way of chain termination) causes apparent inhibition of a chemical reaction.\*

We discuss in this book only positive catalysis which is usually classified as this:

(a) homogeneous catalysis, in which the reaction mixture and the catalyst are either in the liquid or in the gaseous state;

(b) heterogeneous catalysis, in which the catalyst is present in the solid state, whereas the reactants are solutions or gases (this is the most commonly encountered type of catalysis, and it is realized at the interphase);

(c) enzymatic catalysis, in which complicate protein substances accelerate vital reactions in vegetable tissues and living bodies. (Enzymatic catalysis can be both homogeneous and heterogeneous, but this type of catalysis is characterized by certain specific properties, and for this reason it should be classified into an independent type.)

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\* Below we discuss a more complicate case, the role of the medium.



## Chapter Two

### A Few Words About Industrial Catalysis

"I remember the day when we carried out fractionation according to Engler. The condensate had contained 67 per cent of engine petrol. We waited till late at night to collect enough fuel to try it in a racing car, but we were worried that the petrol yield was high and that the engine would possibly knock. I shall never forget my excitement in the morning when the car climbed up hill without any knocking."

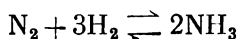
*E. Houdry, 1957*

These words belong to Houdry, the outstanding investigator in the field of practical catalysis. He said them at the International congress on catalysis in 1957, i.e. twenty years after the event when the long and laborious research had at last resulted in the development of an entirely new method of converting heavy petroleum residues into a high-octane motor fuel. The method is now known as the catalytic cracking of petroleum. According to Houdry the idea of catalytic decomposition of hydrocarbons to low-molecular products boiling at lower temperatures occurred to him as far back as in 1927. And it was only a decade later, that aluminosilicates were first used as catalysts in industrial catalytic cracking of petroleum. After 1937 the catalytic methods of petroleum refining, involving a multitude of various chemical processes, have become commonly used everywhere in the world. The main catalytic methods are: the splitting of the carbon-carbon bonds and isomerization of primary products of splitting (cracking); dehydration and isomerization of hydrocarbons with formation of branched and aromatic molecules (reforming); hydrogenation of unsaturated hydrocarbons with simultaneous removal of sulphur and nitrogen as hydrogen sulphide and ammonia (hydrofining); introduction of hydrocarbon fragments into the benzene ring of aromatic compounds (alkylation).

It should be remembered that before 1937 petroleum would only be cracked by the thermic method: petroleum fractions were treated at temperatures of about 500 °C and pressures of 50-60 atm. Catalytic cracking of petroleum is realized at temperatures of 450-500 °C and under atmospheric pressure in the presence of bentonites or artificial aluminosilicates. The products of this process are high-octane fuel and aromatic hydrocarbons, which are valuable intermediates. About one third of the world's stock of engine fuel is produced by petroleum cracking. It should also be noted that over one quarter of the world's total chemical output is produced from various petroleum products.

'Geography' of catalysis is extraordinarily wide and varied, lasting from the manufacture of bulky organic substances whose output is measured in thousands of tons to the control of vital biochemical processes in a living cell (and possibly also to controlled nuclear synthesis). Catalysis is the field of intense research in many branches of the science. It should be understood that we do not consider our task to name all fields of application of catalysis and shall give only some examples from chemical industry.

We can start, for example, with the problem of binding the nitrogen of air, a very inert substance, that reacts with oxygen only at temperatures as high as 3500-4000 °C. Natural resources of bound nitrogen are limited, whereas agriculture requires immense amounts of nitrogen compounds. At the same time resources of free nitrogen are practically unlimited. The chemical way of binding nitrogen into a more reactive substance is as this:

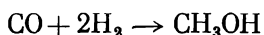


High temperature and pressure are required to make the rate of this reaction practicable. But with growing temperature, the equilibrium of the reaction is gradually shifted towards the formation of the initial substances. On the other hand, if the reaction temperature is lowered and the equilibrium is shifted towards the formation of ammonia, the rate of the reaction decreases markedly. Trying to find a compromise between these two opposing factors, Haber (1907) derived an industrial method by which a mixture of nitrogen and hydrogen was converted into ammonia at a temperature of 500 °C and a pressure of 300 atm. At the present time this is the main method of synthesizing ammo-

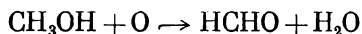
nia which is widely used in the manufacture of fertilizers, nitric acid (catalytic oxidation of ammonia over platinum), ammonium salts, soda, hydrocyanic acid, etc.

At the same time, if more efficient catalysts (compared with the Haber iron catalyst) had been available, the process temperature and pressure could have been decreased and the yield of ammonia increased. This important economical problem drew attention of many chemists in the world. First successes in the low-temperature binding of nitrogen were attained by the Soviet scientists M. Ya. Volpin, V. B. Shur, and A. E. Shilov, who discovered stoichiometric reactions in which nitrogen is reduced to ammonia and hydrazine at normal temperature and pressure conditions.

Using catalysis one can hydrogenate unsaturated chemical compounds. Thus, the treatment of carbon monoxide with hydrogen in the presence of zinc-chromium catalysts at a temperature of 400 °C and a pressure of about 300 atm gives methyl alcohol:

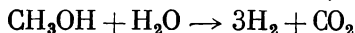


which is a popular solvent and starting product in the manufacture of other valuable substances. For example, oxidation of methyl alcohol on a silver or a copper catalyst gives formaldehyde:



which is also a very important substance used in large quantities in the synthesis of plastics.

Methyl alcohol can be used in the manufacture of hydrogen as well:



Hydrogenation of vegetable oils in the presence of nickel gives solid fats (e.g. margarine). Hydrogenation of coal powder in the presence of sulphides of molybdenum, nickel or tungsten at 400 °C and 200 atm destroys the complicated molecular structure of coal to give a liquid mixture of hydrocarbons that can be used as an engine fuel (Bergius, 1913). The 'Berginization' of coal has not however been used on an industrial scale because fuels obtained from petroleum are much cheaper. But providing a process by which coal could advantageously be hydrogenated into a liquid fuel is an important problem of the near future.

Catalysis is used to accelerate hydrolysis of polyatomic organic compounds, mainly vegetable compounds containing carbohydrates. Mineral acids are used as catalysts here. When a vegetable material (wood wastes, shells of sunflower seeds, cereal straws, etc.) is treated with a mineral acid, polysaccharide chains are destroyed (in cellulose, pentosans) to give foods and fodder, glucose, xylose, furfural, and many other derivatives containing oxygen. If the acid hydrolysis and catalytic hydrogenation are combined in a single process (hydrogenolysis) and the process conditions are made more rigid (about 200 °C, 50 atm), products of deep cleavage of molecular chains, such as glycerol, ethylene glycol, propylene glycol, are obtained. These substances are used in the manufacture of explosives, glyptal resins, and also plasticizers and solvents.

The production of polymers and synthetic fibres should also be mentioned. The pride of the Soviet science is the method of synthesizing rubber developed by S. V. Lebedev in 1932 (ethyl alcohol → butadiene → polybutadiene). Catalytic reactions in this process are effected at the first stage of the process (dehydrogenation and simultaneous dehydration of ethyl alcohol). At the time being butadiene and isoprene are also obtained by dehydrogenation of hydrocarbons of normal structure on aluminochromium catalysts (e.g. from butane). Synthetic rubber can thus be produced from natural gas and also from waste gases of the petroleum refining process.

The discovery of Ziegler-Natta catalysts (1952) has become an important event in the manufacture of polymers. An example of such a catalyst is a mixture of triethylaluminium and titanium tetrachloride. Macromolecules having a certain spatial configuration of its monomer units can be obtained with these catalysts. Articles manufactured out of these polymers possess excellent performance. An extremely active catalytic system developed by Morton (1947) should also be mentioned. It is known as the Alfin catalyst, and is actually a mixture of allyl sodium, sodium isopropylate, and sodium chloride. Butadiene is polymerized within a few minutes in the presence of Alfin to give chains containing scores and hundreds of thousands of monomer units.

Catalysis has to play an important role in the solution of the most urgent problem of nowadays, protection of environment. As Cousteau once said, the earth is like a car

without an exhaust pipe lonely running in space. In fact we cannot dispose of our wastes except into the same environment we live in. Quite a distressing theme, but we have to discuss it since man can already feel the adverse effects of its own activities which in many respects are uncontrolled. Air is poisoned with engine exhausts, wastes of chemical and many other plants, boiler plants, which discharge huge amounts of noxious substances, carbon black, and dust into the air. Batten has thus characterized the situation: "Either people take action to decrease the amount of smoke in the air, or the air will take action to decrease the number of people living on the earth."

Investigators in the field of catalysis work hard to solve the problem of waste disposal. They have developed special devices in which harmful components of exhaust gases of internal combustion engines are burnt out over catalysts. Special catalysts and conditions for decontamination of chemical wastes have been developed. Catalytic filters are made in the form of cartridges filled with a metal gauze or ceramic packing onto which catalytic agents are applied. Such filters operate at temperatures of 250-350 °C.

When we mentioned the temperature and pressure under which catalysis is realized in industrial conditions, we partly meant to compare them with temperatures and pressures of similar chemical reactions that occur in plants and animals. In a living cell, either plant or animal, catalysis is effected at a much faster rate and at normal temperature and pressure. This is attained with biological catalysts, the products of an indefinitely long evolution of life on Earth which has resulted from millions of errors. Probably we shall not soon find out the intricate part along which Nature has passed in the search for effective organic structures having the fantastic power to accelerate processes in living organisms in mild conditions, while we have to spend immeasurably greater efforts, much time and means to realize catalytic processes in industrial conditions. It is quite possible that without knowing it, man repeats the work done by Nature in the search for effective catalysts.

How do we select a suitable catalyst? A scientist would characterize this method as one of trial-and-error. At first sight this method appears quite simple. Substance A is taken and tried for its power to accelerate the wanted reaction. If the substance proves effective, its useful properties

are further developed, and if it fails to accelerate the reaction, it is put aside and substance B tried instead. The investigator tries, errs, and tries again.

True, a modern investigator is in a better position than his predecessors were 60-70 years ago. A vast empirical experience in the field of catalysis has been accumulated and hundreds of thousands of substances of various nature and chemical composition tried for their catalytic power. Therefore, in the development of many important processes, the objective of an investigator is rather improvement of properties of known catalysts. But this problem is not an easy one either. The investigator today still has no general principles, or a kind of algorithm, that would guide him in the purposeful quest of a better catalytic system. Ashmore may be right when he says that most improvements in the field of industrial catalysis are the result of thoughtful experimentation rather than of theoretical developments.

The way out of this situation is a systematic and time-consuming investigation of simple catalytic reactions of various kinds with subsequent establishment of quantitative and qualitative regularities that correlate the nature and structure of a catalyst with its power to alter the rate of chemical reactions. Our book will be devoted to this aspect of the problem. Admitting that our readers are mostly beginners in chemistry (who would possibly devote themselves to catalysis), we decided to begin with some basic principles of physical and physico-organic chemistry, to show how they are used in the study of catalytic reactions, and what results they bring about.

## Chapter Three

### Rate of Reaction

Hinshelwood would say that the reaction kinetics is the field that borders on chemistry and pure physics, and upon which physicists and chemists live without full agreement.

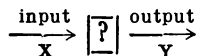
Let us begin our discussion of the kinetics of chemical reactions with some general considerations since according to Gourvits, it is always more difficult to come into detail than to generalize.

Rearrangement of chemical structure is the process occurring within a certain lapse of time and consuming energy. To be more accurate, there are no instantaneous processes in nature, even at the level of elementary particles. Therefore a reacting system, a catalytic system including, can as a rule be characterized by three subsequently interconnected states:



This is the most general representation of the reaction dynamics, and it unfortunately gives no practical hints. To make it operative it is necessary to fill factual material into it, to introduce a certain measure of changes of all states, and to try to formulate the law of changes of these states.

We could also represent the chemical process in the form of a popular 'black box'



We do not know what the box contains but can make conjectures when we observe how the box output responds to the

variations at the box input. But this abstract model is only suitable for general considerations.

The concept of the 'black box' was offered by the English mathematician Ashby and proved effective in studying complex phenomena. The operating principle of the 'black box' consists in determining the response (to the external action) of the object in question whose structure is completely unknown to the investigator. By changing the character of the exciting action on the object we can establish the functional connection between the excitation and the response of the object. But this relationship does not give any information on the structure of the object. If we want to know the exact mechanism we have to dismantle the box (provided we have suitable tools). Once we manage to disassemble the box we discover another box inside it, though less in dimensions but even more black than the first one.

It should be noted, however, that there are methods that can do without opening the box. These are physical methods. Suppose we want to know the structure of a molecule. Then we avail ourselves of a suitable source of electromagnetic radiation and irradiate the substance in question. Under the action of electromagnetic oscillations, electrons and atoms of the molecules start oscillating. The excitation shows itself in the spectrum of radiation at the output. Modern theoretical physics can now connect the observed (macroscopic) changes in the spectrum with the molecular (microscopic) parameters of systems under study.

Let us return however to the former scheme. The teaching of dynamics of chemical processes is divided into two major fields, viz., thermodynamics studying equilibrium of chemical conversions and heat effects that accompany these conversions, and kinetics which treats of the rate of these conversions.

To perceive the essence of catalysis, one should be acquainted with the general principles of these two fields of physical chemistry.

The metaphor of Hinshelwood, the Nobel Prize winner (1956), that we mentioned at the beginning of this chapter, should not be disregarded and one must always remember that the methods underlying calculation of reaction rates, much as they seem to be identical to the methods used in classical mechanics, cannot always be the same successful as in studying mechanical processes.



Motion of a point in space is described by physicists through the concept of velocity of motion, with differentiation of mean and instantaneous speeds of motion. Let us remember that the mean velocity is the change of path per unit time, i.e. the ratio of a section of the trajectory  $\Delta l$  to the interval of time  $\Delta t$ , spent to cover this path. If we decrease  $\Delta l$  and  $\Delta t$  simultaneously and monotonously we shall attain a certain definite value (though both intervals tend to zero) known as the instantaneous rate.

The rate of reaction in chemistry is the change in the number of molecules of the reactants per unit time, i.e. the ratio of the change in the concentration  $\Delta c = c_2 - c_1$  to the interval of time  $\Delta t = t_2 - t_1$ . If we want to be more exact, we must bring said intervals to zero as in the case above. Then we shall obtain a certain limit value which will describe the magnitude of the instantaneous rate of a chemical reaction:

$$(\Delta c / \Delta t)_{\Delta t \rightarrow 0} = dc/dt = W$$

The law of mass action (Guldberg and Waage, 1867) occupies the central place in the teaching of the chemical kinetics: the rate of a chemical reaction is proportional to the product of concentrations of the reactants (all other conditions being the same). This means that if two substances, A and B, enter a chemical reaction, and the resultant product is substance C:



the reaction rate is proportional to the product of concentrations of A and B and does not depend on the amount of product that has accumulated by the moment of time  $t$ :

$$W = -k[A][B] \quad (1)$$

The proportionality factor  $k$  is known as the rate constant which naturally does not depend on the concentrations of A and B. The minus indicates that the concentrations of the reactants decrease in the course of the reaction. If the resultant substance C is unstable and tends to fall into the starting components, then



and according to the Guldberg-Waage law the expression

will be modified into the following:

$$W = -k_1 [A][B] + k_2 [C] \quad (2)$$

In the former case (1) the reaction ends at the moment when both substances, A and B, completely turn into C. In the latter case (2) the reaction stops when the rate of the forward reaction becomes equal to that of the reverse reaction:

$$k_1 [A] [B] = k_2 [C] \quad (3)$$

This state of the reacting system is known as the state of equilibrium. It is usually characterized by the equilibrium constant  $K_{eq}$  which is equal to the ratio of the rate constants of the forward and backward reactions:

$$K_{eq} = k_1/k_2 = [C]_{eq}/[A]_{eq}[B]_{eq} \quad (4)$$

(The symbol 'eq' denotes here that concentrations of substances in equilibrated mixtures are used.)

According to the definition that we gave at the beginning, the rate of the reaction is the limit of the ratio of  $\Delta c$  to  $\Delta t$ , i.e. the first derivative of concentration with respect to time. Therefore, Eqs. (1) and (2) can be modified as this:

$$d[A]/dt = d[B]/dt = -k[A][B] \quad (5)$$

$$d[A]/dt = d[B]/dt = -k_1[A][B] + k_2[C] \quad (6)$$

It does not matter here, which of the starting substances, A or B, is used for determining the rate. The result will be the same since concentrations of A and B change equally per unit time. There is another fact that matters here: we can practically measure only concentrations of substances and cannot determine instantaneous rates of chemical conversions. For this reason, before determining the rate constants (which is the final object of the kinetic experiment) we must integrate the differential equation (5) or (6). If the initial concentrations of A and B are equal (we shall designate this concentration  $[A]_0$ ), then Eq. (5) will have the following form:

$$d[A]/dt = -k[A]^2 \quad (7)$$

and its solution (integral) is as this:

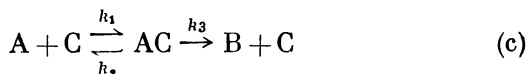
$$1/[A] - 1/[A]_0 = kt \quad (8)$$

From the kinetic experiment we know the value of  $[A]_0$  and its current concentration  $[A]$  at the moment of time

$t$ . We can therefore act as follows: plot  $1/[A]$  against the axis of ordinates and  $t$  against the axis of abscissas; the resultant straight line helps us find the angular coefficient which, according to Eq. (8), is equal to the rate constant  $k$ . The section of the axis of ordinates dissected by the straight line is equal to  $1/[A]_0$  but this value is not important to us for the time being.

When solving the problem on a sheet of paper everything seems quite easy: substances A and B are mixed together, the concentration of one of them is determined at discrete moments of time, the data obtained are plotted in a graph, and the rate constant determined. It is much more difficult to do it practically, because actual chemical reactions follow more intricate paths than model reactions, and a chemist must learn to predict this path from experimental data. An investigator would usually act as follows: a most probable scheme of the reaction is proposed, a system of differential equations compiled, and the system is then solved and the obtained kinetic equation checked for agreement with the experimental data. If there is no proper agreement, a new scheme is invented and a new system of differential equations compiled. The system should not be too complicate since otherwise difficulties will arise in integration.

We now consider how the kinetics of a chemical reaction in the presence of a catalyst C can be described. The calculating principle can better be illustrated by a simple example: consider a monomolecular conversion of a substance A into a substance B. Assume that the reaction will be easier to realize in the presence of a catalyst C through formation of an intermediate product AC. A quickly combines with C but the intermediate AC slowly turns into the final product. This suggestion simplifies the calculations and, moreover, is not far from reality. Let us write the reaction scheme:



In accordance with this equation the expression for the observed reaction rate is

$$W = k_3 [AC] \quad (9)$$

As a rule we cannot measure the concentration of AC and shall therefore exclude it from Eq. (9). In the new formula

we shall have the observed values of  $[A]$  and  $[C]$  (that can always be determined). Let us act as follows. Remember that part of the catalyst is in the free state (as  $[C]$ ), whereas its other part is bound (into  $[AC]$ ). The material balance equation will then be

$$[C]_0 = [C] + [AC] \quad (10)$$

Moreover, we assumed that the formation ( $k_1$ ) and decomposition ( $k_2$ ) of the intermediate substance  $AC$  is fast. The equilibrium constant  $K_{eq}$  for the first reversible stage can therefore be incorporated:

$$K_{eq} = [AC]/[A][C] \quad (11)$$

The expression for  $[AC]$  can be found from formulas (10) and (11):

$$[AC] = K_{eq}[A][C]_0/(1 + K_{eq}[A]) \quad (12)$$

Now substitute it in Eq. (9):

$$W = k_3 K_{eq} [C]_0 [A]/(1 + K_{eq}[A]) \quad (13)$$

True, we could take into account the material balance for the substance  $A$  from the very beginning as well:

$$[A]_0 = [A] + [AC] \quad (14)$$

but this would complicate the equation for the reaction rate. If the concentration of  $A$  is high compared with that of  $C$  (which is usually so in practice), there is no need in taking into account Eq. (14).

Consider Eq. (13). The reaction rate will increase with growing concentration of  $A$  approaching a limiting value. This limit will be attained on the condition that

$$K_{eq}[A] > 1 \quad (15)$$

after which growing concentration of  $A$  will not change the reaction rate (a case of the zero order of reaction). This will occur at high concentration of  $A$  but only on the condition that the constant  $K_{eq}$  is high too. With small values of  $K_{eq}$  and  $[A]$  (so small that the inequality

$$K_{eq}[A] < 1 \quad (16)$$

holds true) the reaction rate will grow in proportion with the concentration of  $A$  (the first order of reaction):

$$W = k_3 K_{eq} [A][C]_0 \quad (17)$$

It is only in this case that we can determine the rate constant.

Since we deal with a simple monomolecular reaction, for which the reaction rate is proportional to the concentration of A (law of mass action)

$$W = k_{\text{obs}} [A] \quad (18)$$

we can compare Eqs. (17) and (18) to make sure that the proportionality factor  $k_{\text{obs}}$  (observed rate constant) is

$$k_{\text{obs}} = k_3 K_{\text{eq}} [C]_0 \quad (19)$$

(The product of the rate constant for the conversion of the intermediate substance AC and the equilibrium constant of the formation of this compound at the first stage of the reaction.)

We could act also in a different way, without assuming equilibrium at the first stage. The only thing that should be preserved is the idea that the concentration of the intermediate compound AC so negligibly changes in the course of the reaction that practically

$$d[AC]/dt = 0 \quad (20)$$

(condition for stationary reaction). Let us make out the expression for AC using (c) and the law of mass action

$$d[AC]/dt = k_1 [A] [C] - (k_2 + k_3) [AC] \quad (21)$$

According to Eq. (20) this expression is equal to zero. Therefore, if we solve the obtained algebraic equation for [AC], we have

$$[AC] = \frac{k_1}{k_2 + k_3} [A] [C] \quad (22)$$

As in the case above, we substitute (22) in the expression for the reaction rate, Eq. (9), to find

$$W = \frac{k_1 k_3}{k_2 + k_3} [A] [C] \quad (23)$$

Whence the observed rate constant is

$$k_{\text{obs}} = \frac{k_1 k_3}{k_2 + k_3} [C] \quad (24)$$

If the constant  $k_3$  is much lower than  $k_2$ , one can disregard it in the denominator of (24). Then

$$k_{\text{obs}} = k_3 \frac{k_1}{k_2} = k_3 K_{\text{eq}} [\text{C}] \quad (25)$$

and we derive the expression similar to Eq. (19) though by a slightly different way.

All these operations may seem tedious and troublesome for those who did not deal with the kinetics of chemical reactions before. But all these calculations are necessary for profound studying of properties of reacting systems since they give us a quantitative measure of reactivity of substances and also confidence in that our knowledge of the mechanism of the process is close to reality.

## Chapter Four

### Energy Barrier

"It has long been known that in nonionic reacting systems in general the rate at which molecules react is less than the rate at which they collide. Arrhenius explained this fact by postulating that molecules cannot react unless at the moment of collision they possess energy in excess of a critical value ( $E$ ) in which case they are called 'active molecules'."

*A. Remick, 1945*

The kinetic experiment would be incomplete if the investigator should limit himself to the determination of the rate constant. The quantitative assessment of the rate of a chemical reaction, however accurate it might be, does not in itself contain any information on the 'intimate' chemical acts occurring in the system. It would be simple to study these acts if we had powerful optical instruments for direct observation of the movement of atoms and transformations in the electron structure of the reacting molecules. But there are no such instruments and only one way out remains—to develop the theory of elementary chemical acts. We must invent an atomic model and try to derive an equation for the dynamics of changes occurring in molecules during a chemical reaction. There exists such a theory. This is the theory of absolute rates of reactions, which was started in 1931 by Polanyi. We shall acquaint ourselves closer with this theory below, and meanwhile let us consider another law of chemical kinetics, known as the Arrhenius law (1889). The law discloses the relationship between the rate constant of a chemical reaction and a certain energy that is characteristic of a given reaction, known as the 'activation energy' and denoted by the symbol  $E$ :

$$k = k_0 e^{-E/RT} \quad (26)$$

where  $k_0$  is the constant or pre-exponential factor,  $R$  is the gas constant (1.987 cal/mole per degree),  $T$  is the Kelvin temperature, and  $e$  natural logarithm base.

In order to find the activation energy  $E$ , the rate of reaction at various temperatures is examined, and the rate constant is found for each  $T$  value. Since Eq. (26) contains two unknown quantities,  $k_0$  and  $E$ , let us act as this. Take the logarithm of Eq. (26),

$$\ln k = \ln k_0 - E/RT \quad (27)$$

construct a plot of  $\ln k$  against  $1/T$  and determine the angular coefficient, which is equal to  $E/R$ . Decimal rather than natural logarithms are normally used:

$$\log k = \log k_0 - E/4.575 T \quad (28)$$

(The latter number is the module for conversion of natural logarithms into common, multiplied by the value of  $R$ , equal to 1.987.)

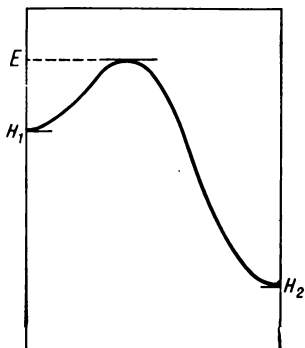


FIG. 1. Energy barrier of a chemical reaction.

The Arrhenius law is connected with a well known symbolic method of representation of the path of the reaction in the form of an energy curve shown in Fig. 1. The meaning of this diagram is as this: to be excited from state  $H_1$  to state  $H_2$ , molecules should possess a certain amount of inner energy that should not be less than a certain critical value  $E$ . States  $H_1$  and  $H_2$  are thus separated by a certain energy barrier whose height is equal to the activation energy  $E$ . The lower the barrier, the higher the rate of reaction in accordance with the Arrhenius equation. The growth of the reaction rate is not unlimited and even in the absence of the barrier ( $E = 0$ ) the reaction occurs at a certain definite (not indefinitely high) rate, since at  $E = 0$ ,  $e^0 = 1$  and  $k = k_0$ .

An important property of the energy curve is that the starting  $H_1$  and the final  $H_2$  levels do not depend on the barrier height. The height of the barrier  $E$  can be altered arbitrarily (provided we know how to do it practically), but the levels  $H_1$  and  $H_2$  will remain unaltered if certain conditions are maintained (temperature, pressure, etc.). In other words, there are various paths along which mole-



cules can move from one state into another, including those states at which the energy barrier is equal to zero. The case where  $E < 0$  is only impossible.

It is important to know what is necessary to initiate a reaction with the least possible expenditure of energy, but we do not know it yet. To be more accurate, we do not know it 'theoretically'. But as far as the practical aspect of this problem is concerned, everything seems quite clear. Experience shows that we can force molecules of the reactants to jump from state  $H_1$  to state  $H_2$  by a more advantageous method, provided a suitable catalyst is available. Now we have come to face closely the 'energetic' interpretation of catalysis: introduction of a catalyst into a reaction mixture without changing the starting and the final level of the system lowers the energy barrier to increase the rate of the reaction under given conditions. Since the rate constant depends exponentially on the height of the barrier the decrease of the latter by 1 kcal/mole increases the rate of the reaction 10-20 times. If the barrier decreases by 5-6 kcal/mole, the rate constant increases dozens of thousands of times. The effect is quite obvious. But how can a suitable catalyst be found?

## Chapter Five

### The Law of Conservation of Disorder

—No, Gods could not have created all that surrounds us.

—Who you think then created the world?

—The eternal motion of matter and combination of invisible molecular bodies.

—If atoms could create such a multitude of various shapes why then could they not once arrange themselves into a house or a shoe?

*Lucretius Carus, Cicero*

Why, in fact, could not atoms once crowd into a shoe? If this is possible in principle, why then does it not happen? If it is impossible, why then Nature has created far more complicate and perfect organisms in the vegetable and animal world?

If the Epicureans, in addition to atoms, the existence of which they guessed, had known anything about entropy, the problem of creating a shoe (as well as of tossing printing types of the Greek alphabet into Iliad) would probably have not been disputed by them.

As de Montaigne put it, the problems that troubled the ancient philosophers “were an incredible collection of absurdities that went by the name of human wisdom”.

But the concept of entropy was formulated only twenty five centuries later. It was done by the German scientist Clausius (1870) who thus started the second law of thermodynamics. But we must first revive in our memory the first law of thermodynamics. It can be formulated in different words but this will not alter its essence: energy cannot be derived from nothing or disappear to nowhere. When applied to heat processes, this law states that the change in the internal energy of a system  $U$  is equal to the amount of heat given to this system less the work  $A$  done by the system:

$$\Delta U = U_2 - U_1 = Q - A$$

It follows then that the amount of internal energy transferred to a system that does not produce any work is equal precisely to the amount of heat.

There are various forms of energy, but its transition from one form into another is done in strictly equivalent proportions. Table 1 gives conversion factors for various forms of energy.

Table 1

Commonly Used Units for Measuring Energy and Their Conversion into One Another

Unit	erg	eV	cal/mole
1 erg	1	$6.241 \times 10^{11}$	$1.441 \times 10^{16}$
1 eV	$1.602 \times 10^{-12}$	1	$2.308 \times 10^4$
1 cal/mole	$6.941 \times 10^{-17}$	$4.332 \times 10^{-5}$	1

It is very important now to determine the values of  $Q$  and  $A$  for various processes. It was assumed that when a system acquires heat,  $Q > 0$ , and when it gives off heat,  $Q < 0$ ; if the system produces work,  $A > 0$ , and if the surroundings work on the system, then  $A < 0$ . Enthalpy (heat content)  $H$  of a system is in the general case\*  $H = U + A$ . As a system is expanded in the process of heating, the work  $A$  is equal to pressure  $P$  multiplied by the change in the volume,  $A = P\Delta V$ .

Absolute magnitudes of enthalpy are unnecessary to us and the difference in these values during transition from one state into another will only matter:  $\Delta H = H_2 - H_1$ . For reactions occurring under constant pressure  $\Delta H$  is equal to the heat effect of the reaction.

The quantity  $\Delta H$  does not depend on the way by which the system is transferred from state  $H_1$  to state  $H_2$ . Reactions occurring with liberation of heat ( $\Delta H < 0$ ) are known as exothermic and those with absorption of heat ( $\Delta H > 0$ ), as endothermic reactions.

The second law of thermodynamics states that, in a closed system, only those processes occur spontaneously that are associated with the increasing entropy  $S$ . The process then continues until this function attains a certain maximum value. Unlike in the case with energy, it is not easy to perceive the physical meaning of entropy. Energy (or work)

\* Numerically  $\Delta H$  can be equal to  $\Delta U$ , i.e. to the change in the internal energy,  $\Delta A$  being zero.

can always be expressed as a product of two parameters, one of which can be described as intensity (potential) and the other extensity (capacity). In the formula  $A = P\Delta V$ , the pressure  $P$  is the intensive parameter and the volume  $\Delta V$  the extensive parameter. Heat, being a form of energy, can also be represented as the product  $Q = T\Delta S$ , where  $T$  performs the role of the intensive parameter and  $\Delta S$  of the extensive parameter.

To describe the physical sense of entropy, this most important concept of thermodynamics, it is not enough to say that entropy is the factor of extensity. Let us consider the statistic interpretation of the function  $S$ , suggested by Boltzmann in 1897. He regarded entropy as being connected with probability of state  $V$  of the system in given conditions:  $S = k\ln V$ , where  $k$  is the Boltzmann constant, which is equal to the ratio of the gas constant to the Avogadro number ( $k = R/N = 8.314 \times 10^7 / 6.024 \times 10^{23} = 1.38 \times 10^{-16}$  erg/g).

The probability of state  $V$  is the number of possible arrangements of particles with respect to one another that can be admitted for a given state of the system. For example, the number of ways in which molecules in a solution can be oriented with respect to one another is much greater than in the crystal state, and the entropy of a solution, or liquid in general, is therefore greater than the entropy of a crystal. In the latter case, atoms (molecules) are packed within a crystal lattice and deprived of freedom of their movement with respect to one another. Hence transition of the crystal state into liquid should be accompanied with an increasing entropy. As far as spontaneous processes in a closed system are concerned, the application of the second law to the increasing entropy indicates the physical transition of the system from a less probable to a more probable state. Gases, liquids, and solutions are characterized by a greater probability of uniform distribution of all particles throughout the volume occupied by the system. Spontaneous accumulation of particles of one kind in one part of the volume and of particles of another kind in the other part of this volume is hardly probable. This will be prevented by the heat motion of particles that interferes with their orderly movement. One can state therefore that entropy is a measure of disorder in a system. As R. E. Peierls once said "... it is easy to shuffle a pack of cards, but it takes much more trouble

le to rearrange the cards in their proper sequence. It is easy to convert an orderly state of affairs, in which we have sugar in one jar and salt in another, into a disordered state in which the two have been mixed together. It is particularly impossible to go back from the disordered state to the ordered one. The impossibility of unscrambling an omelette is a familiar metaphor. In shuffling a pack of cards or mixing sugar and salt, or scrambling an egg, we are increasing entropy."

The degree of disorder increases with the temperature in the system, while the amount of heat consumed to make disorder can be assessed by the formula  $Q = T\Delta S$ , since the product of temperature and entropy is measured in the units of energy:  $\text{erg} \cdot \text{degree} / \text{degree} = \text{erg} = 2.39 \times 10^{-8} \text{ cal} = 2.39 \times 10^{-11} \text{ kcal}$ . This is the amount of heat (energy in the general case) that cannot be used to perform useful work.

In all processes, chemical reactions including, part of energy ( $T\Delta S$ ) is lost with no apparent result. The difference between the general changes in the enthalpy in the course of a chemical reaction and the proportion of unproductive loss was named by Gibbs as free energy and is defined by the expression  $\Delta G = \Delta H - T\Delta S$ .

There are various ways of evaluating free energy, but we shall limit ourselves to the expression  $\Delta G = -RT \ln K_{\text{eq}}$ , from which it follows directly that for reversible chemical reactions, the equilibrium constant  $K_{\text{eq}}$  should first be determined and then its natural logarithm taken and multiplied by  $RT$ . Substituting for  $R$  and  $T$  (assume the standard temperature being  $25^\circ \text{C}$ ), we have  $\Delta G = -1370 / \log K_{\text{eq}}$ .

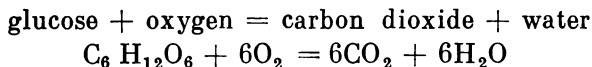
Spontaneous reactions are characterized by the negative meaning of free energy  $\Delta G$ . The positive sign of  $\Delta G$  indicates that the reaction cannot occur spontaneously in the given conditions. If  $\Delta G$  is zero, this indicates that  $K_{\text{eq}} = 1$ . In exothermic reactions the heat effect  $\Delta H$  is negative. If the reaction, in addition, increases the disorder in the system, the difference of the entropies  $S_2 - S_1 = \Delta S$  is positive, whereas the proportion of unproductive loss of energy (item  $T\Delta S$ ) is, naturally, negative. Free energy will therefore be characterized by a greater negative value than in cases where the reaction is accompanied with increasing degree of order. (In this case  $S_2 - S_1$  is a negative value, and the share of unproductive energy  $T\Delta S$  is positive.) Thus, the degree of conversion of reactants in a chemical reaction,

that depends on the equilibrium constant  $K_{eq}$ , is higher with greater heat effect  $\Delta H$  and with greater degree of disorder of particles in the system.

The reader could not but notice that the components of the free energy (enthalpy component  $\Delta H$  and entropy component  $T\Delta S$  in the expression  $\Delta G = \Delta H - T\Delta S$ ) can 'work' in opposite directions, while the direction in which the reaction proceeds in a closed system depends on the higher absolute magnitude of the component. For example, if a reaction is endothermic ( $\Delta H > 0$ ) and the particles are brought into disorder, ( $\Delta S > 0$ ), then, with  $|\Delta H| < |T\Delta S|$  the reaction will occur although it is not advantageous from the aspect of heat effect.

On the contrary, if the reaction is exothermic, ( $\Delta H < 0$ ) but the degree of disorder in the arrangement of particles increases ( $\Delta S < 0$ ), when with  $|\Delta H| > |T\Delta S|$  the reaction will not occur spontaneously although it is favoured by the energy aspect.

It should be added that the methods of thermodynamics of reversible reactions have been so well developed that an investigator can calculate beforehand the changes that will occur in the enthalpy and entropy during rearrangement of the molecule structure and thus evaluate the probability of a reaction in the wanted direction under given conditions. For example, in the reaction of complete oxidation of *D*-glucose in normal conditions (25 °C, atmospheric pressure, aqueous medium):



the free energy change (the free energy of the reaction products less the free energy of the starting substances, assuming all  $\Delta G$  values being negative) is:

$$\begin{aligned} 1 \Delta G_{\text{A}}^{\circ}(\text{glucose}) &= 1 (+ 219.2) = + 219.2 \\ 6 \Delta G^{\circ}(\text{oxygen}) &= 6 (0.0) = 0.0 \\ 6 \Delta G^{\circ}(\text{carbon dioxide}) &= 6 (-92.3) = -553.8 \\ 6 \Delta G^{\circ}(\text{water}) &= 6 (-56.7) = - 340.2 \end{aligned}$$

---


$$\Delta G = - 675.8 \text{ kcal/mole}$$

We have obtained a high negative value for the free energy. Whence it follows that oxidation of glucose in the given

conditions is realizable thermodynamically, while the reverse process (synthesis of glucose molecules from  $\text{CO}_2$  and  $\text{H}_2\text{O}$ ) in this closed system is impossible. We can also establish what conditions are required to render this reaction realizable, but thermodynamics fails to predict the rate at which this process will occur. This is so because the energy levels of the starting and final states ( $H_1$  and  $H_2$ , see the diagram in Fig. 1) are by no means connected with the height of the barrier, whereas it is the activation energy  $E$  that determines the rate of the reaction (Arrhenius equation).

## Chapter Six

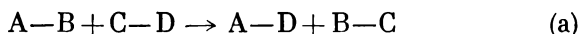
### Overcoming the Energy Barrier

"Pedestrians shall walk on the sidewalk of a street or road only."

From *Traffic Rules*

The Arrhenius law is the experimentally proved fact. It states that the rate of a chemical reaction increases with temperature for the majority of cases, but it says nothing about the way by which the energy barrier is overcome by the reacting system. It is necessary however to make the problem more clear by introducing certain model concepts.

Let us imagine a simple exchange reaction



If we could divide the process of interaction of molecules into separate elementary acts, namely into the cleavage of old bonds A—B and C—D and formation of new bonds B—C and A—D, the picture would be as this: first the reacting system absorbs energy from its surroundings to break the existing bonds, and then it gives off the energy liberated in the formation of new bonds. Diagrammatically it could be represented by a curve whose maximum would correspond to the energy of dissociation of the old bonds (Fig. 2).

In reality the activation energy is always less than the energy of dissociation. Hence the reaction proceeds so that the energy of rupture of the bonds is partly compensated by the energy liberated during formation of new bonds. Physically this might be as follows. As atoms B and C approach each other a bond B ... C is formed and the bonds A—B and C—D are loosened. During this process, energy partly 'transfers' from one section onto another. It is clear that at a certain moment of the process, as the reacting atoms approach each other, all bonds, sooner or later, will be



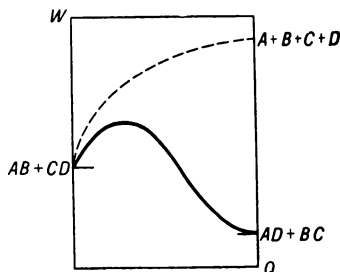
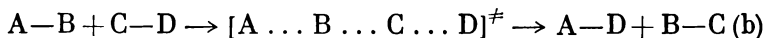


FIG. 2. Measuring energy in the exchange reaction  $AB + CD \rightarrow AD + BC$ . The parameter  $Q$  (the reaction coordinate) characterizes the motion of the interacting atoms as the old chemical bonds are broken and new bonds formed.

equally loose. Polanyi and Eiring call this the 'transition state' and attribute all properties of normal molecules to it, except that the oscillations of atoms by the line along which the atoms move towards each other and the bonds break down (the line is known as the coordinate of the reaction) result in the formation of the products.

For these considerations, it is reasonable to incorporate a certain transition state into the scheme:



that would correspond to the summit of the energy barrier. Only those molecules can reach the summit that possess a certain amount of internal energy. They acquire this energy in the collision with other molecules. Those of them that do not acquire sufficient energy fall back to replenish their store of energy. The ascent to the pick is the most difficult section of the path, but as soon as the molecules reach the summit, they irreversibly roll down. The greater the quantity of molecules that reach the summit, the higher is the reaction rate. These simple considerations make it possible to represent the rate constant as the product of two values, viz.,  $k = a^{\ddagger} K^{\ddagger}$ , one of which,  $a^{\ddagger}$ , is the constant of a mono-molecular conversion of an activated complex into reaction products, measured in frequency units, whereas the other,  $K^{\ddagger}$ , is the equilibrium constant of the formation of the transition complex. Without going into calculations, consider

the final expressions:

$$a^\ddagger = kT/h \quad (29)$$

$$\Delta G^\ddagger = -RT \ln K^\ddagger \quad (30)$$

where  $k$  is the Boltzmann constant,  $h$  is the Planck constant, equal to  $6.625 \times 10^{-27}$  erg·sec.

The expression (30) is already familiar to us. It binds the equilibrium constant of any reversible process with free energy. In the given case  $\Delta G^\ddagger$  can be interpreted as the free activation energy, i.e. the energy required by a reacting system to pass into the transition state. Taking into account expressions (29) and (30), the equation  $k = a^\ddagger K^\ddagger$  can be modified into its final form:

$$k = \frac{kT}{h} e^{-\Delta G^\ddagger/RT} \quad (31)$$

We have one more step to make—to assume that the process of transition into the activated complex obeys the basic relationship of thermodynamics of reversible reactions:

$$\Delta G^\ddagger = \Delta H^\ddagger - T\Delta S^\ddagger \quad (32)$$

where  $\Delta H^\ddagger$  and  $\Delta S^\ddagger$  have the sense of the enthalpy and entropy of the system transition into the activated complex.

Substituting Eq. (32) in Eq. (31), we have

$$k = \frac{kT}{h} e^{\Delta S^\ddagger/R} e^{-\Delta H^\ddagger/RT} \quad (33)$$

It can be shown that  $\Delta H^\ddagger = E - RT$ . (At room temperature the term  $RT$  is not important. For example, at 300 °K, i.e. at 27 °C,  $RT = 1.987 \times 300 = 600$  cal/mole = 0.6 kcal/mole, while for chemical reactions, the activation energy is usually 10-30 kcal/mole.) Comparing Eq. (33) with the empirical Arrhenius law, one can arrive at a conclusion that the pre-exponential factor  $k_0$  is expressed via the entropy of activation,  $\Delta S^\ddagger$ :

$$k_0 = \frac{kT}{h} e^{\Delta S^\ddagger/R} \quad (34)$$

At normal temperature (300° K), the first factor in the  $kT/h$ , the frequency factor, is  $6.3 \times 10^{12}$  sec<sup>-1</sup>. To assess the entropy of activation, the formula derived from Eq. (33)

is used:

$$\Delta S^\ddagger = 4.576 \log k_0/T - 49.2 \quad (35)$$

(Here the entropy is expressed in cal/degree · mole, temperature in °K, and time in seconds.)

The reader will notice that the use of the theory of the transition state is not actually connected with special experiments aimed at determining activation parameters of the reaction, i.e. the entropy and enthalpy of activation. The character of experiments remains the same, viz., the study of reaction kinetics at various temperatures of the medium, calculation of the temperature factor and the activation energy, and finally, of the pre-exponential factor  $k_0$ . But since the pre-exponent in the Arrhenius equation is connected directly with the entropy of activation through Eq. (34) it becomes possible to assess quantitatively this new characteristic of the system. Once it is known, a more detailed understanding of the elementary chemical acts and the geometry of molecules at the summit of the energy barrier can be attempted. In the general case the path of the reaction from the reactants to the products can be different, i.e. it can run via various summits (magnitudes of the activation energy). But as a rule the reaction passes along one (or a small number) of the paths where the consumption of energy will be minimum. The easiness of passage is the criterion for the 'traffic regulations' of the reaction. We discuss this point in more detail in Chapter Twelve.

## Chapter Seven

### What Next?

Larger fleas bear smaller fleas on their backs that feed upon them, and these smaller fleas bear still smaller ones upon them, and thus to infinity.

*From philosophical views of the Renaissance period*

Now we come to a question, what an elementary chemical act is? It can be defined as rearrangement of the electronic structure of the reacting atoms, and then the problem of reactivity and catalysis might be regarded from the point of view of the physics of the electron. But in order to propose a theory and make conclusions based on this concept, it is necessary to find a method to measure the process of electronic reconstruction. Does the study of kinetics of chemical reactions offer such information? Here we have to consider the classical kinetic experiment, which can be described in general as this: (a) the study of the dependence of the reactant concentration on the reaction time and, wherever necessary, construction of experimental kinetic curves; (b) the determination, by a suitable method, of the rate parameters (the order of reaction and the rate constant) of the reaction and calculation of kinetic curves based on these parameters (if the curves well agree with the experimental data, the conjectured mechanism is close to reality); (c) the study of the dependence of the rate constant on temperature (in some cases on pressure as well) and calculation of the main activation parameters, i.e. values of the energy and entropy of activation.

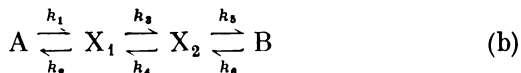
High accuracy of measuring kinetic parameters can be attained but how do these evaluations relate to the dynamics of the electron cloud? After all, the reaction rate and the rate constant, the energy and the entropy of activation are macroscopic parameters. Socrates used to say that it was difficult for a man to know so little of geometry as to be

only able to survey a plot of land. If we follow him, the available information will be quite sufficient to describe the changes in the concentration of all reactants in the given experimental conditions. But all these parameters are statistical in their nature, i.e. they characterize mean properties of the collection of the immense number of particles. Moreover, can we be absolutely sure that we have chosen the true kinetic scheme by which the chemical reaction proceeds? The history of kinetics contains a multitude of examples showing that reactions, that had been considered simple, proved later to be far more complicate. Furthermore, the investigator would often consciously assume a simpler method to calculate the parameters, since he knows that otherwise he can come to a deadlock in his calculations.

Let us assume that we investigate a monomolecular reaction of the type  $A \xrightleftharpoons[k_2]{k_1} B$ , the rate constants being  $k_1$  and  $k_2$ . Our instrumental possibilities are limited to accurate measurement of concentrations of A and B. We take the known kinetic expression for reactions of this type and determine the constants  $k_1$  and  $k_2$  to find out that these parameters well describe the reversible conversion of A into B. Now the instrumental technique is improved as we detect a third substance  $X_1$  in the reaction mixture. This is an intermediate between A and B. Hence we have to reconstruct the reaction scheme and to write as follows:



We make out a system of differential equations (which is always a simple task) and then integrate it. And now we come to a conclusion that it is impossible to determine all rate constants from one kinetic curve. But suppose we managed to do it and a certain additional information concerning the reaction is obtained. Still we cannot feel sure that we have studied the reaction to the end and, in fact, it often happens that in a lapse of time an incontrovertible evidence appears to show that still another component,  $X_2$ , takes part in the reaction, this new component being intermediate between  $X_1$  and B:



Another system of equations is now compiled, but it contains six rate constants. It is very difficult to solve such a system and in some cases becomes only possible with computers. What next? If we continue investigating this reaction, we may, by a lucky chance, succeed in discovering still another component, standing somewhere in between  $X_2$  and B, but then all begins anew.

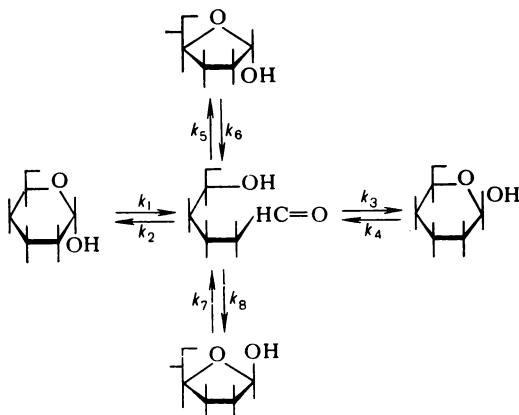


FIG. 3. Isomeric conversions of monosaccharides caused by spatial rearrangement of one hydroxyl group (glycoside hydroxyl) relative to the plane of pyranose or furanose ring.

We have just described a real and, moreover, quite a common situation occurring in chemical reactions. If we did not want to make this long story shorter, we could give another example, using isomerization of carbohydrates (Fig. 3).

We have discussed the mechanism of an uncatalyzed chemical reaction. And what if the reaction can only be effected in the presence of a catalyst? Stages incorporating catalysts should then be introduced into the scheme. In other words, the deeper we go in detail in constructing an accurate solution for determinacy, the sooner do we arrive at a conclusion of impossibility of such a solution. To overcome this pessimistic moods, one must try to find a method that can be used for a tentative but correct assessment of the rate parameters. The method of stationary concentrations (Eq. (20)) seems to suit the purpose since it is the

slowest stage, that is the most decisive factor for the entire kinetics of the process. But it is not reasonable to maintain our illusions with respect to  $k_{\text{obs}}$ . We must abandon the idea of drilling a hole to the centre of the earth since according to Voltaire, "whatever the truth at the bottom of a well may be, it is very difficult to dig the well itself".

The situation is however not so hopeless as it seems at first sight. Beside kinetic methods of investigating elementary chemical acts, there are other methods of studying reacting systems. The following physical methods are among them: optical spectroscopy, radiospectroscopy, roentgenographic and roentgenostructural analyses, mass-spectrometry, the study of dispersion of optical and magnetic rotation. Information obtained by these methods, and processed appropriately, makes it possible to give us an insight into the world of elementary interactions of electrons and nuclei. And in order to conceive the chemical transformations at the atomic-molecular and electron levels, it is necessary to introduce certain microscopical concepts of the structure of molecules and to try to understand macroscopic properties of reacting systems as the results of the internal characteristics of molecules. This is a very important and fascinating moment in the study of chemical reactions. It is hardly possible to imagine that a chemical investigator could refuse the pleasure of constructing a molecular mechanism of the reaction in question. But only those who know the bitter taste of disappointment can understand the difficulty of this trip into the inner world of 'elementary acts'.

## Chapter Eight

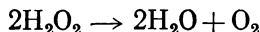
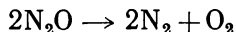
### Model Reactions

"Sabatier, and later many other investigators in the field of catalysis, suggested their explanations of the mechanism of reactions. I myself am the author of three conjectures, and at least two of them must therefore be incorrect .... It is quite possible that all the three will prove erroneous."

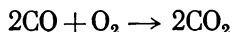
*E. Rideal, 1957*

It is hardly reasonable to study the mechanism and regularities of catalysis on examples of such complicate processes as hydrogenation of coal (Bergius method). In their investigation chemists use simpler chemical reactions which they call 'model' reaction. The following reactions are examples:

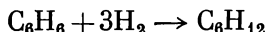
Decomposition of nitrous oxide and hydrogen peroxide



Oxidation of carbon monoxide (a very important reaction for decontamination of exhaust gases of internal combustion engines):



Hydrogenation and dehydrogenation of benzene and other interconversions between saturated and unsaturated molecules:

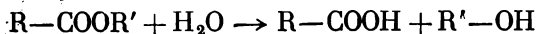


Decomposition of formic acid:



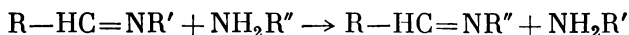
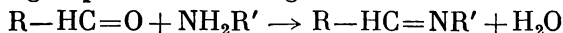
Anomeric conversions of monosaccharides and their derivatives (see Fig. 3).

Hydrolysis of alkyl halides and esters of carboxylic acids:





Reactions of nucleophilic addition and substitution at the carbonyl group and its analogues:



Ortho-para conversion, isotope exchange of hydrogen, molecular rearrangements, inversion of sugar, hydration of unsaturated compounds, reactions of carboxylation and decarboxylation, hydrolysis of acetal bonds in simple molecules and high-molecular compounds can also be attributed to this kind of reactions.

Prolonged and systematic study of reactions of this type made it possible to develop certain concepts about the mechanism of conversions, to postulate important empirical rules, and to follow up the dynamics of accumulation and disappearance of various intermediate compounds. As a result, in interpreting mechanisms, the investigators developed a kind of special language and logics that must be studied by chemical investigators before they start unassisted voyage in the vast ocean of modern catalytic organic chemistry.

We now discuss some modern concepts of heterogeneous catalysis. No one doubts at the present time that the chemical conversion of molecules is preceded by their adsorption at the interphase, that is the surface on which two different phases border, for example, solid (crystalline) and gas phases. As soon as the chemical reaction proper is completed, the product of this reaction is isolated into the gaseous phase (desorption). Both processes can be measured to a high degree of accuracy and these measurements permit the kinetics of the reaction to be followed. The processes occurring at the surface can be assessed by the change of concentration of the reactants in the gas (or liquid) phase. It is possible however to make a general conjecture that molecules collide with superficial atoms to form intermediate compounds or unstable complexes. The structure of the complexes can be most varied, but one thing is definitely clear: only those parts of adsorbed molecules will undergo electronic rearrangement that are brought in direct contact with the atoms of the surface, since the radius of action of chemical forces is of the same order of magnitude as the dimensions of the atoms. Academician A. A. Balandin (1928) named these contacting parts 'multiplets'. Figure 4 shows some of the

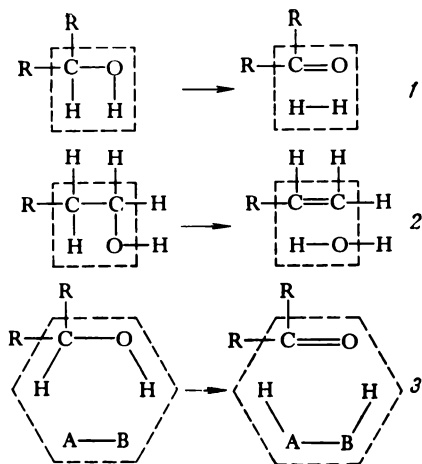


FIG. 4. Dehydrogenation (1) and dehydration (2) of alcohols and also reduction (3) of a hypothetical compound A—B in accordance with the multiplet theory of catalysis.

conjectured mechanisms of reconstruction of atomic structures constituting multiplets. Atoms and chemical bonds of a multiplet are, for the sake of convenience, placed inside a square or a hexagon. Atom groupings that do not participate directly in the reaction acts (the extra-index substitutes) are brought outside the polygon. It does not mean that they are not important for catalysis. On the contrary, they can substantially change the reaction course, e.g. by the intramolecular effect that they produce on the electron state of the reactive centres, and hence on the affinity of these centres for superficial atoms of the catalyst.

Figure 4 illustrates the modern concepts of the scientists about the reactions of dehydrogenation and dehydration occurring on the catalyst surface. The sketch is rather self-explaining. It is only a more or less good illustration of our concepts about the reconstruction of the chemical structure the result of which is, as always, the break down of old and formation of new chemical bonds. To make this scheme useful, it should be completed with such physical ideas that would admit quantitative checking. Principles of structural and energetical correlation are such ideas.

Now that almost 50 years have passed since the origination of the idea of multiplets, the following two circumstances stand out clearly. Firstly, a solid surface will only function as a catalyst when the distance between atoms in the reacting grouping of the molecule corresponds to the interatomic distance in the crystal lattice (which is prerequisite but not at all sufficient). Secondly, the bonds between the atoms in the reacting grouping and the superficial atoms should not be either too weak or too strong. In the former case the bonds in the reacting grouping will not be weak enough, and in the latter case the products of decomposition will act like 'poison' (the energy correlation principle).

In contrast to the scheme shown in Fig. 4, these two postulates make it possible to carry out some quantitative calculations. For example, taking into account the interatomic distances of C—O (1.43 Å) and C—C (1.54 Å), one can be sure that in order to accelerate the reaction of dehydrogenation, catalysts in which the distance between their atoms is slightly smaller than that in the catalyst for the dehydration reaction, should be selected.

The energy correlation principle consists, after all, in taking into account the energy balance of the reaction. In other words, it is the sum of energies of the breaking and newly forming bonds and the energies of chemical bonds of all atoms of the multiplet with the atoms of the catalyst. From the qualitative point of view, it is clear enough that if all existing bonds are first to be broken and only then new bonds formed, this would require much energy, equal at least to the sum of energies of the broken bonds. Catalysts reduce the initial energy requirements by forming intermediate bonds with atoms of the reacting molecules. True, these bonds should not be too strong since otherwise the process will be terminated at the stage of formation of superficial chemical compounds.

The multiplet theory suggests several simple mathematical expressions showing the dependence of the height of the reaction energy barrier on the energy of bonds between the molecules and the atoms of the catalyst. It follows from these equations that the minimum activation energy corresponds to a certain optimum energy of bond between a molecule and the catalyst. Once we have the quantitative information on the heat of formation of superficial compounds

of various molecules with different catalysts, it might be possible to select a proper catalytic system for a given reaction so that it proceeds with the least consumption of energy. But this should probably require intense preliminary work that would make the problem of 'prediction of catalytic action' an empirical search for values of energies of bonds between organic molecules and solid substances of various chemical nature and structure.

## Chapter Nine

### The Smile of Mona Lisa

"Hinshelwood once named the reaction of oxygen with hydrogen the Mona Lisa of chemical reactions. Once we accepted this comparison, we can extend it to state that the reaction of ethylene with hydrogen on the surface of nickel has perceived the smile of Mona Lisa."

*E. Rideal, 1957*

The reaction of addition of hydrogen at the double bond of ethylene in the presence of various metal catalysts, of which the most active are nickel, platinum, rhodium, and palladium, belongs to the most investigated reactions from the experimental point of view. Perhaps for this reason, the scientists cannot arrive at a definite conclusion as to the intimate mechanism of the reaction occurring on the surface of the catalyst. Is one of the C—H bonds first broken (associative mechanism) or is it one of the double C=C bonds of the ethylene molecule (dissociative mechanism) as shown in Fig. 5? Does the hydrogen molecule require simultaneous activation, and if so, how can it be activated? Do all catalytic surfaces act similarly or does each metal select the mechanism to its own taste?

As usual, the scientists divide into several groups the number of which depends on the number of alternative mechanisms, and a long discussion begins. At last a scientist appears who declares that all mechanisms are valid and we have only to find out why the reaction follows this or that route in each particular case. This tangle of problems could be straightened out if we had more subtle tools at our disposal to penetrate the world of electronic interactions between superficial atoms of the catalyst and the reacting molecules.

As for Mona Lisa, her mysterious smile could be better likened to another reaction, namely mutarotation of monosaccharides, first discovered by Dubrunfaut in 1846 when he measured the change of optical activity of freshly prepa-

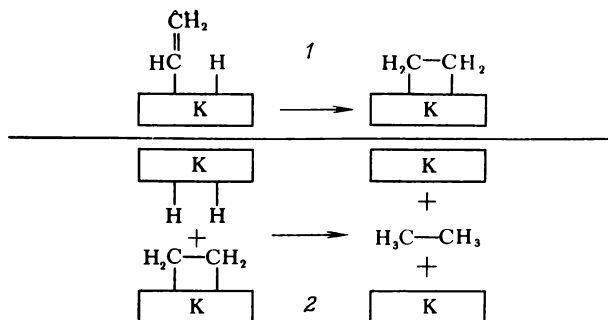


FIG. 5. Adsorption (1) and hydrogenation (2) of ethylene on the surface of the catalyst K.

red solutions of glucose. The reaction in itself is not practically important but it is interesting as a model that can be used for studying regularities of homogeneous catalysis. For this reason more than three hundred papers are devoted to this reaction.

By the present time we have definite concepts on the mechanism of inversion of sugars of this type (Fig. 6). The investigators feel quite sure that the process here consists of many stages, and nevertheless they prefer not to go into detailed calculations of all rate constants.

The main steps of the isomeric change of monosaccharides are as follows: (a) the oxygen bridge  $\text{C}_1-\text{O}-\text{C}_5$  is broken by the action of the molecules of the medium and an inter-

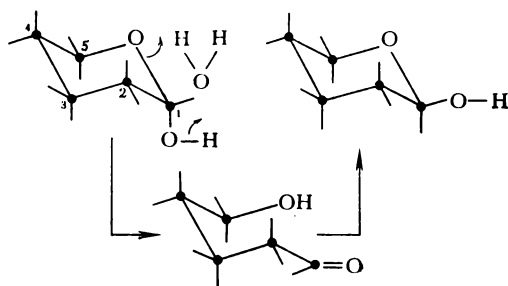


FIG. 6. Mechanism of opening of the monosaccharide pyranose ring in mutarotation, viz., the isomeric conversion connected with rearrangement of the glycoside hydroxyl. The numerals designate the carbon atoms of monosaccharide.

mediate compound with the aldehyde or dihydrate group at  $C_1$  is formed; (b) the terminal group at  $C_1$  turns about the  $C_1-C_2$  bond and the glycoside centre  $C_1$  reacts with the OH-group at  $C_5$  to close the pyranose ring. But the glycoside hydroxyl  $C_1-OH$  is now in the opposite configuration to the plane of the pyranose ring. Thus, the starting and the end compounds differ only in spatial arrangement of the OH-group while the transition between these two states cannot occur without preliminary opening of the carbohydrate ring.

Let us try to consider the mechanism in detail. Assume logically that in order to open the pyranose ring it is necessary to remove only one hydrogen atom (in the proton form) from the hydroxyl at the  $C_1$  and to attach it to the cyclic oxygen with preservation of the valencies of all atoms. It is obvious that an open aldehyde form of monosaccharide will result from such a rearrangement. It is also clear that at the second stage of the reaction (cyclization) the hydrogen atom will be placed where it earlier belonged. The proton can be transported by molecules (one or several) of water, or by any other suitable molecule that can readily donate and accept hydrogen atoms in the form of proton. These are acids and bases (monofunctional, i.e. having one proton donating or proton accepting centre) or amphoteric compounds (bifunctional, i.e. having two centres). If we consider attentively the scheme of the reaction, we shall notice that the one-step transfer of protons with participation of two functional groups of the transporting medium is more effective than the stepwise transport.

In fact, as was shown by Swain and Brown, a molecule of 2-hydroxypyridine is an unusually effective accelerator of mutarotation of glucose (to be more exact, its tetramethyl derivative). This on the whole amphoteric compound increases the rate of mutarotation 5000 times compared with an equimolecular mixture of phenol and pyridine. Although functional groups of the same chemical nature (hydroxyl and a nitrogen atom) participate in the transport in both cases, their mutual presence in one molecule of 2-hydroxypyridine proves to be more advantageous. The advantage does not consist only in that two successive collisions of glucose with phenol and pyridine are replaced by one collision of glucose with hydroxypyridine (although it is not an unimportant fact from the statistic point of view either).

It is most likely that the effectiveness of 2-hydroxypyridine is due to the coordinated transfer of the proton between two pairs of the interacting centres: hydroxyl of the pyridine ring + cyclic oxygen; nitrogen of the pyridine cycle + + hydroxyl at C<sub>1</sub> of glucose.

The result of proton transfer between these centres is the quick opening of the glucose ring and 2-hydroxypyridine acquires an unstable bipolar form that readily returns to the initial state. As far as the coordination of the proton transfer is concerned, it actually means the following: any transfer act is accompanied with a shift of the electron density inside the six-membered complex that favours other transfer acts. It does not matter from what point the process begins: from the transfer of the glycoside proton onto the catalyst nitrogen atom or from protonization of the cyclic oxygen at the expense of the hydroxyl group of the catalyst. What is important here is the synchronism of the proton transfer acts with the acts of redistribution of the valency electrons, which makes it impossible for the reaction to follow another, less advantageous, path (via formation of ionized forms of glucose rich in energy).

The example of catalysis with 2-hydroxypyridine is very popular among investigators working in organic chemistry and catalysis, and it stimulated the development of an extremely fruitful idea of polyfunctional character of molecule activation in ordinary organic reactions and in enzymatic catalysis (to be discussed later). Developed were the concepts of cyclic transition complexes, but the search for other, more effective, catalysts for mutarotation of monosaccharides gave no appreciable results, and 2-hydroxypyridine has remained an unravelled catalyst of the cyclic proton transfer.

We want to emphasize again that in the reaction of isomeric changes of monosaccharides, the decisive role is played by the elementary acts of break down and formation of the bonds, proton-heteroatom (atoms having unpaired electrons), that stimulate deeper structural changes in the molecule skeleton. This is an example of an important group of catalytic processes classified under the name of acid-base catalysis.



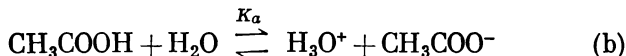
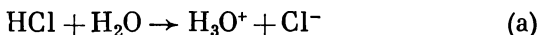
## Chapter Ten

### Acid Catalysis

"In the days of Lavoisier oxygen was the acidifying principle; later hydrogen was considered the carrier of acid properties; but it is becoming increasingly obvious that, although these elements are important, they are not essential to the display of acid properties."

*M. Kilpatrick, 1954*

Adding acid or base into a reaction mixture to accelerate the reaction is one of the most popular methods used by investigators in their work. This is known as acid-base catalysis. We shall limit ourselves only to the 'proton' catalysis in aqueous solutions. Hydroxonium ion  $\text{H}_3\text{O}^+$  acts here as a catalyst. It is formed during dissociation of a mineral or an organic acid in aqueous solution:



When taken in moderate concentrations, hydrochloric acid (a) fully dissociates into ions. Weak acids, acetic acid (b) in particular, do not fully dissociate, and a certain equilibrium between ions and undissociated molecules is established in the solution. A measure of dissociation of these acids is expressed by the dissociation constant  $K_a$ , which for the acetic acid is

$$K_a = [\text{CH}_3\text{COO}^-][\text{H}^+]/[\text{CH}_3\text{COOH}] = 1.75 \times 10^{-5} \text{ mole/lit}$$

(Proton does not exist in the free state in solution, since it easier combines with the molecule of water. For the sake of brevity, we write simply  $\text{H}^+$ , but mean the hydroxonium ion.)

Remember that the concentration of hydrogen ions  $[\text{H}^+]$  is expressed in the units 'gram-ion per litre' (g-ion/litre). For example, during dissolution of one gram-mole of HCl (36.5 g) in one litre of water, the hydrogen ion concentra-

vid is 1 g-ion/litre, since the atomic weight of the proton is unity. For convenience in use, the hydrogen ion concentration is expressed in units of pH:

$$\text{pH} = -\log [\text{H}^+]$$

i.e. in units of the exponent of the  $\text{H}^+$  ion concentration (introduced by Sørensen). The advantage of this method of expressing acidity of a medium becomes quite apparent from the following example. Suppose we study catalysis of a reaction at  $[\text{H}^+]$  from  $10^{-2}$  to  $10^{-5}$  g-ion/litre, and we have to represent graphically the results of the experiment. Let us plot the concentration of  $\text{H}^+$  ion in this range against one of the ordinate axes. Of course, the experimental points should be plotted so that they could be easily interpreted. Assume 5 mm to be a unit of  $[\text{H}^+]$ . Then the whole scale of  $[\text{H}^+]$  will be 5-metre long. Such a roll of paper is difficult to handle. But if we assume the index of pH as a unit, the working length of the scale will be only a few centimetres long.

The table which follows below shows the connection between acid concentration, hydrogen ion concentration, and the corresponding indices of pH:

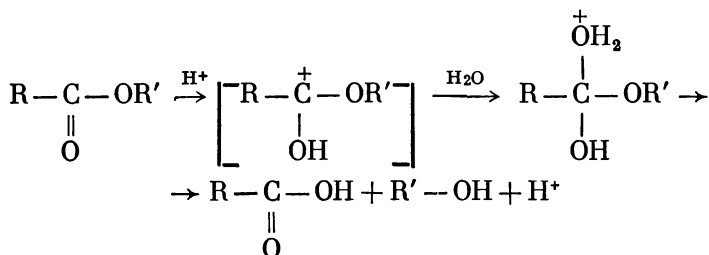
Table 2<sup>-</sup>

Concentration of HCl and  $\text{H}_3\text{O}^+$  Expressed in Various Units

Concentration of HCl, g/mole	Concentration of $\text{H}_3\text{O}^+$ , g-ion/litre	pH
0.1	$10^{-1}$	1.0
0.01	$10^{-2}$	2.0
0.001	$10^{-3}$	3.0

At the present time we are well aware of the mechanism of the activating action of the proton. It is supposed that the first act of catalysis is, in many cases, the transfer of the proton from the hydroxonium ion to the proton-accepting site of the reacting molecule. Heteroatoms act, as a rule, as the proton acceptors in dilute acids. These are oxygen, nitrogen, sulphur, having free (unpaired) electrons. As a result of the protonization, the electron density is shifted from the adjacent centres of the reacting

molecules, and this displacement (bond polarization) facilitates the chemical reaction. Consider the acid hydrolysis of an ester:



In this example, the protonization of the carbonyl oxygen atom promotes subsequent addition of a water molecule to the carbon atom. An unstable 'tetrahedral complex' is formed, which quickly falls into carboxylic acid and a molecule of alcohol with simultaneous regeneration of the catalyst (proton).

At moderate concentrations of acids, the rate of the acid-catalyzed reactions usually increases with the concentration of  $\text{H}^+$  ions:

$$k_{\text{obs}} = k_{\text{H}}[\text{H}^+]$$

where  $k_{\text{H}}$  is the catalytic constant that does not depend on  $[\text{H}^+]$ . There are however reactions in which the increase of  $[\text{H}^+]$  over a certain limit retards progressively the reaction rate. Formation and hydrolysis of the products of interaction of amines with carbonyl compounds are examples of such reactions:

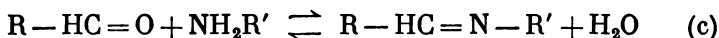
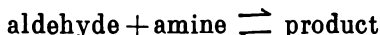
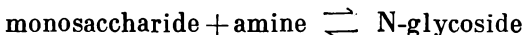


Figure 7 illustrates the dependence of  $k_{\text{obs}}$  on the pH of the medium during formation and hydrolysis of N-glycoside bonds:



This dependence is expressed by bell-shaped curves. Both sides of the 'bell' are almost symmetrical relative to a certain optimum value of pH, at which the rate of the corresponding reaction is maximum. Let us consider the mechanism

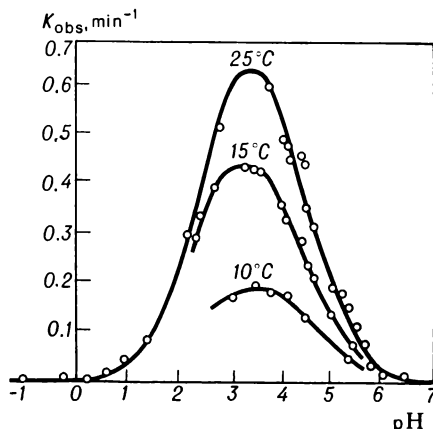
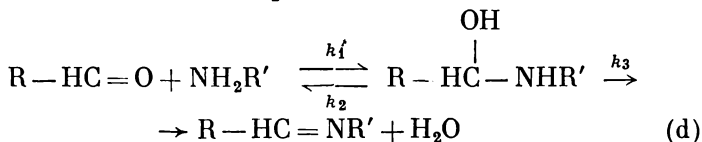


FIG. 7. A bell-shaped curve showing the dependence of the rate constant on pH of the medium. Acid-catalyzed hydrolysis of N-glycoside bond in ethyl ether of N-glycozylglycine:  $-\text{HC}_1-\text{NH}-\text{CH}_2\text{COOC}_2\text{H}_5 + \text{H}_2\text{O} \rightarrow \text{HC}_1-\text{OH} + \text{NH}_2\text{COOC}_2\text{H}_5$ .

of acid catalysis and the mechanism of the reaction on the whole using the stationary concentrations principle as the main method. Our aim will consist in proposing a model of interaction of particles, in deriving a dependence of  $k_{\text{obs}}$  on  $[\text{H}^+]$  based on this model and in comparing the results of preliminary calculations with experimentally obtained data. We shall consider the  $\text{H}^+$  ion as an equal-in-rights participant of the process (c) differing from the main components only in that it will leave the reaction sphere at the final stage.

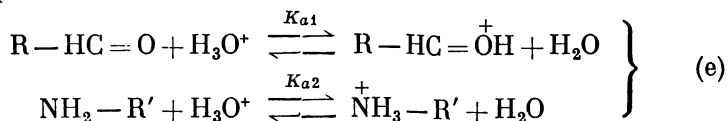
At the beginning of our discussion let us note that, as the experiment shows, the reaction (c) occurs in two subsequent steps: the amino group is first attached at the carbonyl carbon atom to give an intermediate product (amino alcohol) and then a water molecule is eliminated from the amino alcohol to form the end product:



The reaction begins with an attack by the amino group nitrogen atom on the carbonyl carbon which has a certain

deficit in the electron density because the electron cloud is displaced towards the oxygen atom. The carbon atom is not however always cleared so that it can interact with the valency electrons of nitrogen. When we add acid to the reaction mixture, the formed  $H^+$  ions start an attack on the molecules of both partners in the reaction, but it will be only one type of attack, namely the attack on the carbonyl oxygen, that will promote the chemical reaction. The coordination of proton with the oxygen atom will promote further stripping of the carbon atom, and it will readily accept the nitrogen atom electrons. The attachment of the proton to the amino group is undesirable since the protonized forms of amines are chemically inactive because the free electrons of nitrogen are blocked with the proton.

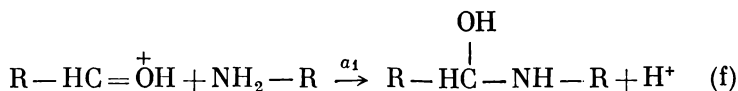
Thus, in conditions of acid catalysis, along with the main reaction (d), side reactions (protolytic) also occur and they should be taken into account in making out kinetic equations:



To give quantitative characteristics we need measures to express proton-accepting power of the oxygen and nitrogen atoms. Dissociation constants  $K_{a1}$  and  $K_{a2}$  characterizing the equilibrium of protolytic reactions (e) can be used as these measures:

$$K_{a1} = [A][H^+]/[AH^+], \quad K_{a2} = [B][H^+]/[BH^+] \quad (36)$$

where A is the carbonyl compound and B is the amine. What follows next, depends on the slowest stage in the reaction (d). Let the slowest stage be the one at which the amine is attached to the protonized aldehyde:



Then, in accordance with the mass action law, the expression for the observed reaction rate can be derived:

$$V_{obs} = a_1[AH^+][B] \quad (37)$$

The total concentration of the components is the sum of the protonized and free forms. Therefore, in order to take into account the share of the active components ( $\text{AH}^+$  and B), introduce the equation of the material balance:

$$[\text{A}]_0 = [\text{A}] + [\text{AH}^+], \quad [\text{B}]_0 = [\text{B}] + [\text{BH}^+] \quad (38)$$

Using Eqs. (36) and (38), find the expression for  $[\text{AH}^+]$  and  $[\text{B}]$ :

$$[\text{AH}^+] = [\text{A}]_0 [\text{H}^+] / (K_{a1} + [\text{H}^+]), \quad [\text{B}] = [\text{B}]_0 K_{a2} / (K_{a2} + [\text{H}^+])$$

Substitute them in Eq. (37), and after incomplicate calculations we have:

$$V_{\text{obs}} = \frac{a_1 K_{a2} [\text{H}^+] [\text{A}]_0 [\text{B}]_0}{[\text{H}^+]^2 + (K_{a1} + K_{a2}) [\text{H}^+] + K_{a1} K_{a2}} \quad (39)$$

Comparison of this expression with the common equation of kinetic reactions of the second order (reaction rate is proportional to the product of concentrations of the reactants A and B) makes it possible to write the expression for the observed rate constant

$$K_{\text{obs}} = \frac{a_1 K_{a2} [\text{H}^+]}{[\text{H}^+]^2 + (K_{a1} + K_{a2}) [\text{H}^+] + K_{a1} K_{a2}} \quad (40)$$

If the slowest stage in the reaction (d) is the dehydration of the intermediate compound, then the expression of  $K_{\text{obs}}$  is as this:

$$K_{\text{obs}} = \frac{a_3 K_{\text{eq}} K_{a2} [\text{H}^+]}{[\text{H}^+]^2 + (K_{a2} + K_{a3}) [\text{H}^+] + K_{a2} K_{a3}} \quad (41)$$

It differs from the previous expression in that the numerator contains  $a_3$  (the rate constant of conversion of the protonized amino alcohol into the end product) and  $K_{\text{eq}}$  (the equilibrium constant of the first step of the reaction) instead of  $a_1$ , and that the denominator contains the dissociation constant of the intermediate product  $K_{a3}$ . Otherwise the equations are similar and expressed graphically by similar curves. Let us analyse one of them, for instance Eq. (41).

It is very difficult to construct a graph showing the dependence of  $k_{\text{obs}}$  on  $[\text{H}^+]$  since the range within which  $[\text{H}^+]$  changes is very wide. It is therefore better to use the pH units. Assume arbitrary constant values for  $a_3$ ,  $K_{\text{eq}}$ ,  $K_{a2}$ , and  $K_{a3}$  and calculate the value of  $k_{\text{obs}}$  for various values of  $[\text{H}^+]$ . Now construct a graph plotting  $k_{\text{obs}}$  against the

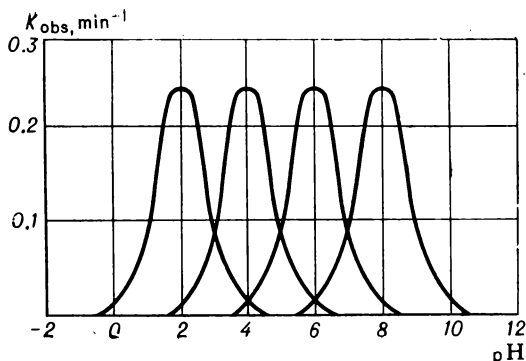


FIG. 8. Dependence of  $k_{\text{obs}}$  on pH, as calculated from Eq. (25) with  $a_s = K_{\text{eq}} = 1$  and  $\text{p}K_{a2} = \text{p}K_{a3} = 2, 4, 6$  and  $8$  (in the order of enumeration of the curves).

axis of ordinates and pH values against the axis of abscissas. A characteristic bell-shaped curve will be obtained (Fig. 8). It is quite similar to those in which experimental data for  $k_{\text{obs}}$  of some studied reactions of amines with carbonyl compounds are plotted. This circumstance makes us think that we are on the right way. What conclusions can be derived from all what we have at our disposal? First and foremost let us make the most of the circumstance that the curves illustrating the dependence of  $k_{\text{obs}}$  on the pH have their maxima at quite definite magnitudes of pH, and hence we can obtain additional information from the experiment, i.e. we can find out optimum values of pH at which the rate of the reaction is maximum. Once we have equations of the type (40) and (41) it is not difficult to determine the physical meaning of the optimum pH. To do so, let us take the first derivative of  $k_{\text{obs}}$  for  $[\text{H}^+]$  and equate the result of differentiation with zero (conditions of function extremum). For the second case (Eq. (41)) we have the following:

$$[\text{H}^+]_{\text{opt}}^2 = K_{a2}K_{a3} \quad (42)$$

whence, after taking logarithms

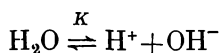
$$\text{pH}_{\text{opt}} = 0.5(\text{p}K_{a2} + \text{p}K_{a3}) \quad (43)$$

where  $\text{p}K_{a2} = -\log K_{a2}$ ,  $\text{p}K_{a3} = -\log K_{a3}$  are the indices of basicity of the starting amine and the intermediate compound (the higher the basicity of the compound, the stronger

does it retain the added proton and the higher is the value of  $pK_a$ ).

Equation (43) shows that the lower the basicity of the proton accepting centre of the molecule, the lower is the pH at which the maximum reaction rate is attained. In other words, with lowering basicity of the reactants, the curves of dependence of  $k_{\text{obs}}$  on pH are shifted to a more acid side. Indeed, with decreasing  $pK_a$  of the reacting molecule, the concentration of the acid-activated (protonized) forms, and hence the reaction rate at a given value of pH, should also decrease. The same holds for the former case, when the reaction rate on the whole is determined by the first stage. In this case the optimum pH will be equal to the half-sum of the indices of basicity of the starting compounds, i.e.  $pK_{a1}$  and  $pK_{a2}$ . Evidently, using the experimentally determined pH optimum, it is possible to estimate one of the  $pK_a$  values, provided the other is known. If both constants are known, e.g.  $pK_{a1}$  and  $pK_{a2}$ , or at least we can guess their approximate values, we can predict, with the same degree of approximation, the range of acidity of the medium, within which the wanted reaction will proceed at an acceptable rate. True, before making any prognosis, one should study properly the conduct of the reaction in various conditions and determine the most probable mechanism of the reactions.

We considered the example of a specific acid catalysis with participation of hydroxonium ions. Basic catalysis is also encountered with in practical investigation. This is acceleration of reactions by the action of hydroxyl ions. As is known, molecules of pure water fall into ions:



and the dissociation constant of this reaction is

$$K = [\text{H}^+] [\text{OH}^-] / [\text{H}_2\text{O}] \sim 10^{-14} \text{ mole/litre} \quad (44)$$

whence, in neutral conditions (without acid or alkali)

$$[\text{H}^+] = [\text{OH}^-] \sim 10^{-7} \text{ and } \text{pH} = -\log 10^{-7} = 7$$

The ionic product of water is often used instead of Eq. (44):

$$K_x = [\text{H}^+] [\text{OH}^-] \quad (45)$$

This can always be used to assess the concentration of the  $\text{OH}^-$  ion against the known pH of an aqueous solution.



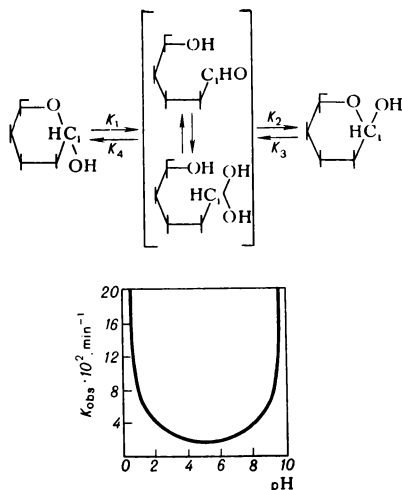
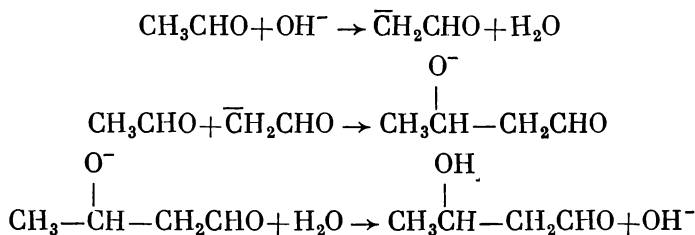


FIG. 9. Isomeric conversion of monosaccharides (mutarotation) and dependence of the rate constant of mutarotation of D-glucose on pH of the medium.

The catalytic action of the  $\text{OH}^-$  ion can be in many cases explained by detachment of the hydrogen atom from the reacting molecule as is, for example, the case with the aldol condensation of acetaldehyde:



Some reactions can be accelerated by both acids and bases. Mutarotation of monosaccharides is an example. This is a reversible isomeric conversion connected with the opening of the carbohydrate ring and transition of the substitute at  $\text{C}_1$  from the axial into equatorial position (Fig. 9). It has long been known that the dependence of the mutarotation rate constant on the pH of the solution is described by a characteristic curve having the shape of an overturned

bell. The dependence is easy to explain. To that end assume that  $k_{\text{obs}}$  linearly depends on the concentration of  $\text{H}_3\text{O}^+$  and  $\text{OH}^-$  ions:

$$k_{\text{obs}} = k_0 + k_{\text{H}}[\text{H}^+] + k_{\text{OH}}[\text{OH}^-] \quad (46)$$

where  $k_0$  is a certain constant,  $k_{\text{H}}$  and  $k_{\text{OH}}$  are the constants of the catalytic action of the ions  $\text{H}_3\text{O}^+$  and  $\text{OH}^-$ . Now substitute  $[\text{H}^+]$  for  $[\text{OH}^-]$  using Eq. (45):

$$\begin{aligned} k_{\text{obs}} &= k_0 + k_{\text{H}}[\text{H}^+] + k_{\text{OH}}K_x/[\text{H}^+] = \\ &= \frac{k_{\text{H}}[\text{H}^+]^2 + k_0[\text{H}^+] + k_{\text{OH}}K_x}{[\text{H}^+]} \end{aligned} \quad (47)$$

The comparison of Eq. (47) with Eqs. (40) and (41) shows that the obtained relationship is a kind of an inverse function of  $[\text{H}^+]$  and should graphically be represented by a curve with a minimum. The position of the minimum of the curve  $k_{\text{obs}}$  versus pH of mutarotation can easily be found from the condition of the function extremum (Eq. (47)):

$$\text{pH}_{\text{opt}} = 0.5(\log k_{\text{OH}}/k_{\text{H}} - \text{p}K_x),$$

where  $\text{p}K_x = -\log K_x$ .

We believe that the amount of examples given will be quite sufficient to show the method by which homogeneous acid catalysis is studied and what conclusions can be drawn from the study of the reaction kinetics at various acidity of the medium. The catalysis with acids and bases is so widely used in organic reactions that it should not be disregarded in discussion of the structure and reactivity of organic molecules. There are investigators, however, who sometimes 'forget' it, and then they arrive at incorrect conclusions as regards the mechanism of molecular rearrangements that occur in chemical reactions.

## Chapter Eleven

### 'Tender Points' of Molecules

"Chemistry would be a much simpler science than it is, if every combined atom or group of atoms carried its physical and chemical properties, or its contributions to such properties, unchanged into all the molecules in which it participates. We know that this does not happen, and that those properties which are especially associated with a given atom or group usually differ appreciably, according to what other groups are present in the molecular structure, and according to the way in which such other groups are bound and located with respect to the given atom or group."

*C. Ingold, 1953*

The question arises whether it is or it is not possible to describe the properties of molecules (any property, the reactivity including) as a simple sum (either algebraic or vector) of properties of separate atoms or groups of atoms. Strictly speaking, it is impossible. But in cases where there is no other way out, one can use the known rules of additivity of properties for a series of organic molecules having similar structures. For example, in the study of the reaction of amine with aldehyde, where the nature of only one component is altered, whereas the other component remains unchanged, it is possible to suppose that with the changing nature of the substitute, the reactivity of the functional group in which this substitute is replaced will monotonously change as well. This holds in fact for the majority of cases.

These observations can quite reasonably be explained from the point of view of physics, provided a molecule is assumed to be consisting of two main units, viz., the reacting centre and a substitute that does not take direct part in the reaction. Since these units are connected with each other, the changing nature of the substitute will immediately produce the change in the electron state, and hence the reactivity of the reacting centre will be modified. The question

now is whether the change is 'regular' and whether a certain measure of influence can be attributed to these units.

Hammett (1935) gave the positive answer to this question. He gave the start to the correlation analysis of organic reactions which is very popular now. The analysis is based on the equation that binds the logarithms of rate constants with a certain parameter  $\sigma$ , characterizing the degree of action of a substitute on the electron state of the reacting centre:  $\log k = A + \rho\sigma$ , where  $A$  is the constant and  $\rho$  is the proportionality factor, which can be considered as a measure of conductivity of the effect that the substitute produces in the given chain of bonds.

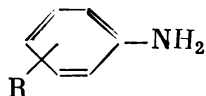
By now parameters  $\sigma$  have been found empirically for many substitute units. Some of them are given in Table 3

*Table 3*

Values of  $\sigma$ -Constant of Substitutes,  $pK_a$  of Amino Group and  $e$  for Aromatic Amines

Substitute R	$\sigma$	$pK_a$	$e$
<i>para</i> -OCH <sub>3</sub>	-0.268	5.44	1.764
<i>para</i> -CH <sub>3</sub>	-0.170	5.16	1.743
<i>meta</i> -CH <sub>3</sub>	-0.069	4.69	1.730
H	0	4.69	1.729
<i>meta</i> -OCH <sub>3</sub>	+0.115	4.30	1.712
<i>para</i> -Cl	+0.227	4.07	1.694
<i>meta</i> -Cl	+0.373	3.60	1.669
<i>meta</i> -NO <sub>2</sub>	+0.710	2.47	1.651
<i>para</i> -NO <sub>2</sub>	+1.270	1.04	1.531

where, in addition to  $\sigma$ -constants of substitutes in the benzene ring of aromatic amines, given also are magnitudes of  $pK_a$  of the amino group and electron density  $e$  (in relative units) of the nitrogen atom of the compound



The constant  $\sigma$  is a quantitative measure of the substitute's ability to pull the electron density from the benzene ring

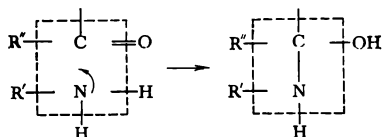


FIG. 10. Reaction of amine with aldehyde.

and the nitrogen atom attached to it. The given data show that with increasing  $\sigma$  constant towards positive values, the electron density on the nitrogen atom decreases, and the basicity of the amino group, expressed by the quantity  $pK_a$ , the negative logarithm of the dissociation constant  $K_a$ , is lowered too.

Let us summarize: the higher the value of  $\sigma$ , the stronger does the substitute pull the electron density off the reacting centre of the aldehyde and amine; a symbolic representation of this process can be seen in Fig. 10.

The picture is approximately as this. If the nature of one of the substitutes, say amine ( $R'$ ), changes so as to follow the growth of the constant  $\sigma$ , the reaction rate should decrease because of the decreasing electron density on the nitrogen atom. And vice versa, if the nature of the aldehyde substitute ( $R''$ ) is changed accordingly, the reaction rate should increase as a result of stronger stripping of the carbon atom.

Is that all what we can take from the Hammett equation? Is it much or little? We must admit that the Hammett equation cannot give us more than it can give in principle: it will not explain the intimate processes of reconstruction of the electron shell, but still it is very useful as an empirical rule. After all it can predict the rate of the reaction for kinetically unstudied systems belonging to those compounds and reactions for which the parameters  $\sigma$  and  $\rho$  are known.

Let us see now what our knowledge of catalysis in the reaction of aldehyde and amine can add to the correlation analysis. As has already been said, reactions of this type occur at least in two stages, each of which can be accelerated in the presence of an acid. The dependence of  $k_{obs}$  on pH is very often expressed in the form of a bell (Fig. 7), whose position depends on the basicity indices of the centres of molecules responsible for the acid activation.

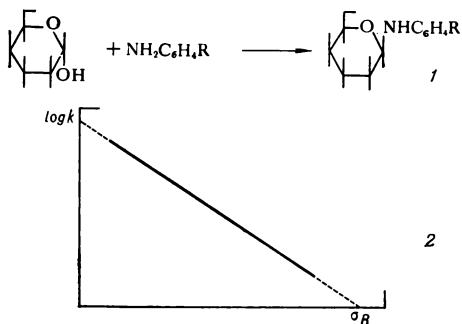


FIG. 11. Formation of N-glycoside bond during reaction of monosaccharides with aromatic amines (1) and dependence of the rate constant of this reaction on  $\sigma$ -constant of substitute R in the benzene ring of arylamine (2). The glycoside centre acts like an analogue to the carbonyl group in the reaction of N-glycosilation.

To rule out the effect of the  $\text{H}^+$  ion concentration on  $k_{\text{obs}}$ , let us assume the rate constant, related to  $[\text{H}^+]$  unit:  $k_{\text{H}^+} = k_{\text{obs}}/[\text{H}^+]$  to be a measure of reactivity. (This case corresponds to the linear dependence of  $k_{\text{obs}}$  on  $[\text{H}^+]$  and corresponds graphically to the beginning of the left-hand branch of the curve showing the dependence of  $k_{\text{obs}}$  on pH.) We can now compare the rate constants for a series of similar amines and see if they agree with the Hammett equation. Consider the reaction of formation of N-aryl glucosides as an example. This is a special case of the reaction of the aldehyde group with amines. The experience shows that the linear dependence with the negative angular factor (Fig. 11) is really observed within the coordinates of the equation. In this particular case we are interested to know why the constant  $\rho$  has a negative sign. It is difficult to answer this question. As is seen from the diagram, the substitute in the benzene ring of the amine should produce different effects on the rate of various stages of the process. As has already been said, at the first stage the increasing electron-accepting power of the substitute should reduce the rate as the  $\sigma$  constant grows. At the second stage (dehydration of the intermediate amino alcohol with simultaneous cyclization of the carbohydrate fragment) the rate will increase because of the stripping of the carbon atom  $\text{C}_1$  that undergoes a nucleophilic attack by the hydroxyl at  $\text{C}_5$ . All depends on which of the stages is the slowest. If this is the first stage,

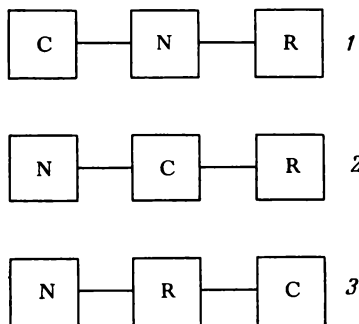


FIG. 12. Three possible modes of arrangement of the reactive centre (C), proton-acceptor (N) and substitute (R).

the sign of the  $\rho$  constant should be negative, and if the second stage, the sign should be positive. Without going into detail, let us note that the second stage is the slowest in our case. The opposite correlation (with the positive sign of the constant  $\rho$ ) should therefore be observed. But in reality this is not so and hence we face a contradiction between the conclusions of the theory and the experiment. How can this contradiction be explained and to what conclusions can it lead us?

Let us begin with the general picture of acid catalysis. We have stated that the essence of this type of catalysis consists in coordination of the proton with the molecule. Once we admit this, we must add another unit into the molecule, namely the part of the molecule that is responsible for the acid activation (in other words, the *proton-accepting centre* of the molecule). We now have three units: the reacting centre, the substitute, and the proton acceptor. All depends on how these three units relate to one another (Fig. 12). If they are arranged in line, only three methods of binding are possible. Two of them are of special interest. By one mode the proton acceptor is located between the reactive centre and the substitute (1) and by the other the reactive centre is found in between the proton acceptor and the substitute (2). In the former case the substitute will affect the electron state of the proton acceptor, which is located closer to it than the reactive unit. And this is important for its coordination with the proton. If the substitute is capable of strongly

pulling the electron density, it will first and foremost strip the proton acceptor and, to a lesser degree, the reactive centre. But stripping the proton acceptor means decreasing the probability of its protonization, and hence retarding the reaction at a given acidity of the medium. And that is just what happens in the acid-catalyzed formation of N-aryl glucosides.

The reaction rate here is limited by the second stage, i.e. by the conversion of amino alcohol into the reaction product, and the structure of the amino alcohol just corresponds to the first method of arrangement of the main units of the molecule: reactive centre (C)—proton acceptor (N)—substitute ( $C_6H_4-R$ ). For this reason, the increasing electron-accepting power of the substitute (increasing the  $\sigma$  constant) decreases the observed rate constant of N-glycosylation. It becomes possible to formulate the following special rule: if the proton acceptor is located across the way by which the electron effects of the substitute are transferred onto the reactive centre, the sign of the constant  $\rho$  in the Hammett equation will, in the conditions of acid catalysis, alternate to the sign that would otherwise be with the proton acceptor located behind the reacting centre, or in case where the reaction would proceed without acid catalysts.

An attentive reader will notice that the idea of the unit structure of organic molecules and the correlation of the reactivity with the structure is not so bad in itself. We must not demand from this theory, which on the whole is phenomenological (descriptive), more than it can give. The reader will not fail also to notice that having begun with the discussion of the elementary chemical acts, we tried to persuade him that the kinetic parameters should be manipulated with great care since they are not a direct measure of elementary acts. The reader can feel a certain disappointment but let it be better a desire to find out why despite the limited information on the elementary acts, chemists are not afraid of using them in their conjectures concerning the mechanisms of reactions. In this connection we should like to remind once again that this is the logical essence of the investigation in chemical reacting systems: the logics permits (if not compels) to use microscopic concepts, the conclusions of which should explain all regularities of changing macroscopic parameters of systems. We have no other way at present and therefore have to reconcile ourselves to it.



## Chapter Twelve

### The Least. What is It?

“Even the ancient philosophers knew that Nature would do nothing in vain, and this well agrees with the concept of the least effort. If Nature were to spend more than the minimum required, then some of her acts would have been in vain.”

*L. Euler, 1753*

Let us have a short look back into the history. The seventeenth century is famous for the origination of fundamental ideas and formation of methodology of scientific thinking. The scene of our retrospect is the French city of Toulouse. Pierre de Fermat, a parliamentary Counsellor (the author of the well known Fermat problem) formulated an idea that started the history of development of principles of mechanics and modern physics: ‘Nature acts by the easiest and most accessible ways.’ In thirty five years Jean Bernoulli offered a problem to mathematicians in the ‘Acta Eruditorum’: “Two points,  $A$  and  $B$ , are given in a vertical plane. Determine the path  $AMB$  along which a body  $M$ , acted upon by the force of gravity, passes from point  $A$  to point  $B$  within the shortest possible time .... By the way, wishing to preclude possible erroneous solutions I should like to emphasize that although a straight line connecting  $A$  and  $B$  is the shortest path between them, the body  $M$  does not cover it in the shortest time, whereas there exists a curve  $AMB$ , well known to those skilled in geometry.

I shall give the solution to the problem if no one else does it before the end of this year.”

This, as G. Leibniz put it, ‘wonderful and unprecedented problem’ was solved by Newton, Leibniz, de L’Hopital, and Jacques Bernoulli, the brother of Jean Bernoulli. At the end of the year, Bernoulli published his own solution of the problem, expressed only in four formulas. The result was as follows: acted upon by the gravity force, the body  $M$  does not pass along the straight line connecting the points  $A$  and  $B$ , but it moves along a curve  $AMB$  which is actually

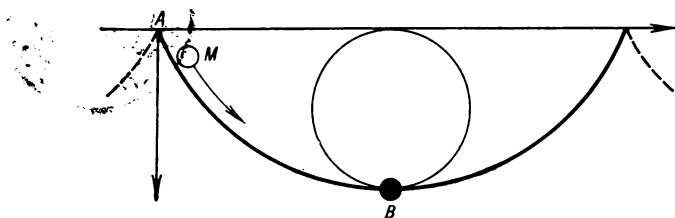


FIG. 13. A cycloid traced by a point on a circle rolling in a plane along a straight line. The specific property of this curve is that the time of travel of the ball  $M$  to the point  $B$  does not depend on the starting position of the ball.

a part of a cycloid, the trajectory traced by a point on a circle that rolls 'upside down' along a horizontal straight line without slipping (Fig. 13). Now everyone knows why a body prefers to travel a longer, cycloidal path  $AMB$ , rather than the shortest straight line  $AB$ . This happens because the curvilinear path of this only possible configuration is covered by the body within the shortest possible time, whereas all other paths will be covered in longer time.

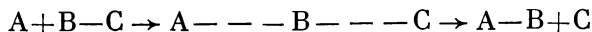
What do we like in this problem and its solution offered by Bernoulli himself? What do this problem and catalysis have in common? Is there any connection between the Bernoulli cycloid and catalysis in organic reactions? We answer 'yes' since the Bernoulli problem lay the first stone in the foundation of the variational calculation in mathematics and variational principles in classical mechanics. Physics often offers problems where the minimum or maximum values for some variables are to be found. The values are known as functionals (e.g. in the Bernoulli problem, the functional is the time of descent of the body). Variational calculation is aimed at the development of methods to solve such 'extreme' problems. Problems in classical mechanics and modern physics are quite varied, but what is in common with all of them is the principle of the 'least action'. A simplified formulation of this principle is as this: among the multitude of ways by which a system can pass from one state to another, actually realizable becomes that way at every point of which the difference between the kinetic and potential energies of the system is the least. Following this principle we can find the optimum solution, provided we know the starting and the final state of the system and the difference (functional dependence) between the kinetic and potential energies.

Now return to the energy barrier of chemical reactions and see whether it is possible to make the problem of its overcoming more clear. As we have already mentioned, the expression for free energy of activation is

$$\Delta G^\ddagger = \Delta H^\ddagger - T\Delta S^\ddagger$$

Formally, the enthalpy is the potential energy, while the entropy component is a measure of kinetic energy of the system. If we assume the principle of the least action to hold for chemical processes, the description of the transition period of the reaction can be limited to variational problems of physics. This approach agrees with the intuitive assessment of the process of chemical reconstruction (whatever it may be, simply chemical or catalytic) as the process following the 'line of least resistance', i.e. with the least possible consumption of free energy. In this sense, a reacting system is like an ideal automatic device that selects only one out of many possible ways where the barrier, separating the starting and the final state, is the lowest. It is difficult to refrain from a commonplace but a very exact comparison: if we have a hill, or better two hills in our way, which way shall we choose to pass them? This depends on the time at our disposal and our moods. If neither favours, we shall not climb the hill to have a good view of the landscape from its summit, but shall rather choose a path that will bring us to our destination at the shortest time. Assume that a reacting system is short of time as well. But we shall not go into mathematical details and only consider the qualitative aspect of the problem.

Remember that from the physical standpoint the entropy is a degree of disorder in a system and hence the greater the number of degrees of freedom the stronger is the disorder. This means, for example, that if in a given system parts of molecules or atoms are bonded between themselves, this process is accompanied with the decreasing entropy, and vice versa. As to the enthalpy, let us assume that when a new bond is formed in the transition state, part of energy that is liberated in this process is consumed to break the old bond. Bearing in mind these two aspects, let us consider a simple three-atom model



and follow the changes in the enthalpy and entropy in this system as A approaches B—C.

It will be enough to consider three versions. Version 'a'—formation of the bond A—B precedes the breakdown of the old bond B—C. Then, as the system approaches the transition state, the entropy should decrease, since the number of progressive degrees of freedom decreases. The difference in the entropies of the transition and starting states should therefore be a negative value:

$$S^\ddagger - S^0 = \Delta S^\ddagger < 0$$

At the same time, the energy liberated during formation of the bond A—B partly compensates the energy consumed to break down the B—C bond. The enthalpy of the transition into the activated state should therefore have moderate magnitudes. The higher the effect of compensation, the lower is the activation energy of the reaction.

Version 'b'—the breakdown of the bond B—C precedes the formation of the new bond. It is evident that as the system nears the transition state, the entropy should increase on account of the increasing number of degrees of freedom, and hence the difference in the entropies must be a positive value:

$$S^\ddagger - S^0 = \Delta S^\ddagger > 0$$

But the consumption of energy to break the B—C bond is not fully compensated for by the inner sources and it follows that the enthalpy of activation must be high (higher than in version 'a', at any rate).

Version 'c'—the elementary acts of formation and breakdown of bonds occur in strict agreement (in synchronism) in that sense that any movement of atom A towards atom B corresponds to an accurately the same amount of movement of atom C from atom B. In this case the loss of degrees of freedom at the expense of bonding the atom A is fully compensated by the formation of new degrees of freedom of the displaced atom C. The difference in the entropies should therefore be zero:

$$S^\ddagger - S^0 = \Delta S^\ddagger = 0$$

whereas the activation enthalpy is, in accordance with Eq. (32), equal to the free activation energy.

What conclusions can be drawn from the considered picture? First and foremost we can feel sure that the components of the free activation energy, enthalpy and entropy, act in opposite directions in the mechanism of substitution. Although the formation of new bonds stimulates the breakdown of old bonds, this transition period can be disadvantageous because of the decreasing entropy. All depends on the conditions of the reaction. In some cases it is more advantageous for a system to follow the path of formation of a new bond, and in other cases, the path of breaking the old one. If we change mildly the conditions of a reaction, in any case so mildly as not to destroy the chemical structure of molecules or the mechanism of movement of the system towards the transition state, the system will choose the optimum version, provided it is left to act to its own discretion (which is not always the case). In other words, sometimes the system chooses version 'a' and in other cases, e.g. version 'b', or something intermediate between them. In this case the system will tend to preserve the value of the free energy of activation at a certain (stationary) level, since this value is the characteristics of the reacting system itself connected with the chemical nature of the reactants. The system sometimes fails to maintain this value at a stationary level as an investigator interferes. But sometimes the reaction conditions change so that the system can preserve the magnitude of the free energy at an approximately constant level (e.g. if the nature of the solvent is changed). Then we can observe a specific effect of mutual compensation of the entropy and enthalpy components of free energy. This proves that the system adapts itself to new conditions and chooses a version of its progress at which  $\Delta G^\ddagger$  remains approximately unchanged.

Figure 14 gives an example of such compensation of the components  $\Delta H^\ddagger$  and  $\Delta S^\ddagger$  for reactions occurring at a glycoside centre of monosaccharides and N-glycosides. We plotted in the graph all known experimental values for various reactions that have only one thing in common, the chemical nature of the reactive centre. Despite the fact that various reactants attack the glycoside centre  $C_1$ , a certain tendency towards decreasing the energy of activation can be traced as the activation entropy decreases. At negative values of

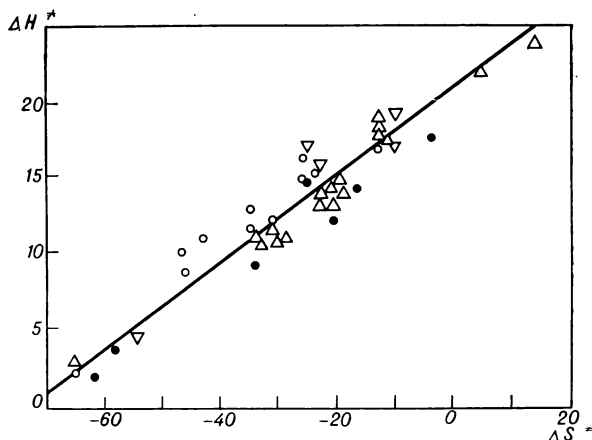


FIG. 14. Isokinetic dependence for reactions of the glycoside centre of monosaccharides and N-glycosides (isomerization, formation, and hydrolysis of the glycoside bonds). Dots indicate experimentally found values for the activation parameters of these reactions.

$\Delta S^\ddagger$ , i.e. when the entropy of the transition state is less than that of the starting state (version 'a'), the energy of activation is lower than in the case where  $\Delta S^\ddagger$  is positive (version 'b'). The point of intersection of the straight line with the axis of ordinates evidently corresponds to version 'c', when the elementary acts occur in strict synchronism. We shall not specify more accurately, what particular elementary acts are meant, since this would lead us too far into the field of the mechanism of reactions of the glycoside centre, while it is not the object of our discussion. We only wanted to illustrate the idea that nature (in our case this is a reacting system) always tends to follow an optimal path from the starting to the final state.

The object of the investigator consists not only in revealing the 'strategies and tactics' of the reacting system but also in proposing conditions under which the wanted reaction could travel a path requiring the least possible energy without branching into side reactions. It is desirable, for example, to find conditions under which a reaction might follow a path requiring the least activation energy and at the same time having a great positive entropy of activation. It follows that we shall probably fail in our attempt to combine these

two conditions by only mildly interfering with the course of the reaction. The external interference must be more rigid, but not to the extent when the reacting system could follow quite a different, unwanted direction. How can it be attained? In the general case we do not know, and act therefore empirically, i.e. we try various versions, err, and try again. It should be noted that biological catalysts act very effectively to solve this problem, but we shall discuss them later.

## Chapter Thirteen

### Homogeneous Catalysis

"Chain reactions of oxidation continue to remain an intensively developing field of scientific and technical research having the immense practical importance."

*N. M. Emanuel, 1971*

Catalysis of chain reactions occupies a special place among the numerous catalytic reactions. "Chain reactions are such chemical and physical processes in which the formation of certain active particles in a substance or a mixture of substances leads to the effect that each active particle produces a whole series (chain) of successive conversions of substance." (Emanuel, 1957).

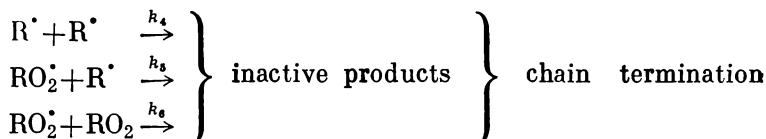
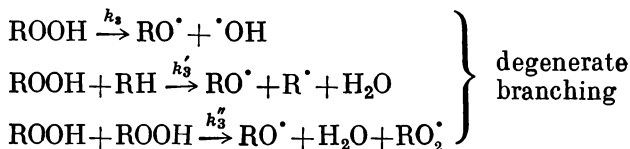
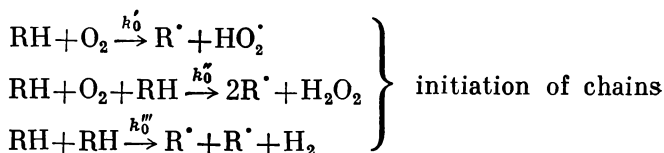
This mechanism of the development of a process becomes realizable because an active particle reacts with a substance to give, in addition to the reaction products, also a new (or more than one) active particle capable of participating in a new reaction, etc. Once initiated chain of conversions of a substance continues until the active particle leaves the system (the active particle is 'destroyed' and the chain terminated). The most difficult stage of the process is the production of active particles (e.g. free radicals), but once they are formed, the chain is easily propagated.

Chain reactions are quite common in nature. Polymerization, chlorination, oxidation, and many other chemical processes have the chain mechanism, and to be more exact, radical-chain mechanism (with participation of radicals).

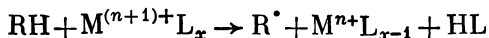
The mechanism of oxidation of organic compounds (at early stages) is well studied today. If we designate a substance to be oxidized as  $R-H$  (where  $H$  is the hydrogen atom that is the least strongly bonded with the remaining part of the molecule  $R$ ), the mechanism of the reaction can be described



as this:

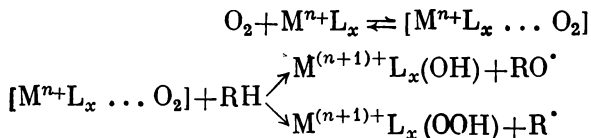


Catalysts, e.g. compounds of metals having variable valency, can produce effect on each of the above stages of the process. Consider a few examples. As catalysts interact with organic compounds (RH), chains are originated at the initial stage of oxidation because of the transition of compounds of metals of higher valency ( $\text{M}^{n+1}$ ) into compounds of lower valency ( $\text{M}^n$ ):



(Here L is, as a rule, an organic substitute, the remainder of an acid or a ligand of a chelate complex, and  $x$  is the number of substitutes in the complex.)

In the presence of oxygen, chains are generated as this:



First, oxygen forms a complex with a compound of a metal of variable valency in its lower state, and then this complex reacts with an organic compound to form radicals and compounds of metals in their higher valency.

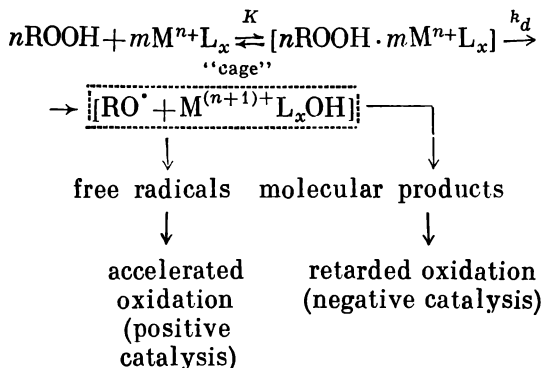
It is evident that these two reactions transfer the metal from its lower valency into higher valency and back. The metal leaves one reaction in the transformed form (i.e. strictly speaking the metal is not a catalyst but rather an initiator of this reaction), but in the other reaction it is returned into its initial state. Such regeneration of a catalyst can take place at other stages of the process as well, e.g. when catalysts take part in degenerate branching of chains (to be discussed later).

The first reaction is proved by the fact that its activation energy does not depend on the strength of the broken C—H bond in the organic compound. Hence the stage controlling the overall rate of the process is not the breakdown of this bond, but the transfer of the electron. The second reaction is proved e.g. by the fact that copper  $\alpha$ -phthalocyanine is a catalyst for oxidation of  $\alpha$ -methylstyrene, although it does not accelerate appreciably the decomposition of hydroperoxide.

We now consider the role of catalysts in the degenerate chain branching processes. The interaction of hydroperoxide with a metal can both accelerate and retard the oxidation of organic substances with compounds of metals of variable valency. This depends on the character of products that are formed in the decomposition of hydroperoxide. Metal compounds react with hydroperoxides to give a complex that falls inside the 'cage' of the solvent (medium). If radicals that are formed during decomposition of the complex escape the boundaries of the 'cage' they initiate the process (positive catalysis). If however these radicals are re-combined inside the 'cage' into molecular inactive products, the radical-chain process will be retarded (negative catalysis),

since the hydroperoxide, the potential donor of new radicals, is spent in vain.

The role played by metals of variable valency in the process of degenerate chain branching can be represented in the general form like this\*:



This mechanism of catalysis is now substantiated quite fundamentally. Intermediate hydroperoxide complexes with compounds of metals of variable valency (falling into free radicals or molecular products) have been detected by both kinetic methods and spectral and spectroscopic methods, whereas the formation of radicals has been established by the inhibition method, chemoluminescence and electronic paramagnetic resonance methods.

For the considered case, the rate of decomposition of hydroperoxide in the presence of a catalyst is described by the equation

$$W_{\text{ROOH}} = \frac{k_d K [\text{ROOH}]_0^2 [\text{M}^{n+}\text{L}_x]^m}{1 + K [\text{ROOH}]_0^2}$$

This formula can be used to calculate equilibrium constant of formation of the complex,  $K$ , the decomposition constant of the complex,  $k_d$ , and the quantities  $m$  and  $n$ , which characterize the number of molecules of hydroperoxide and catalyst that compose the complex.

The accelerating or retarding action of catalysts, metals of variable valency, can be traced in an example of oxidation of many organic substances, e.g. ethylbenzene hydroperoxide; stable at 50-80 °C in the absence of catalysts,

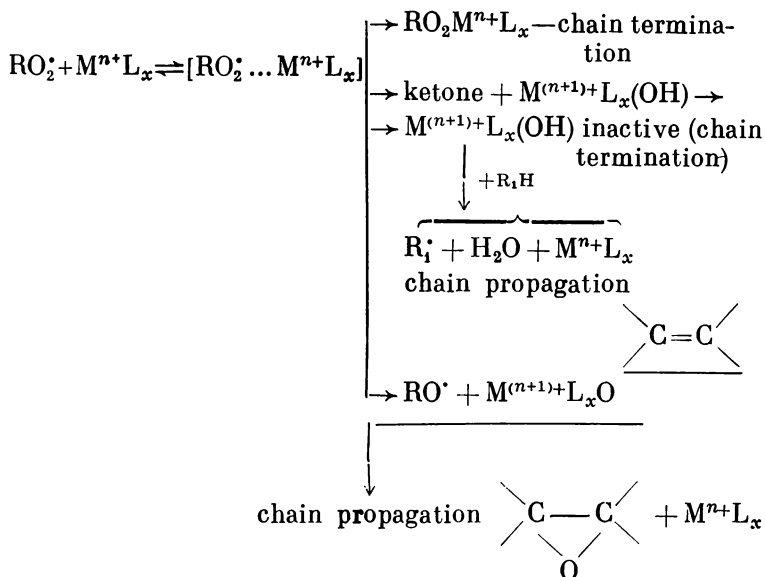
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\*  $m$  and  $n$  are the stoichiometric factors.

it decomposes at a fast rate in the presence of, say, *bis* (alpha-thiopicoline anilide) of copper. Ethylbenzene oxidation in these conditions is markedly retarded since the products of decomposition of hydroperoxide are not radicals but molecular compounds.

Oxidation of tetralin in the presence of palladium *bis*(stilbene dithiolate) is very much similar.

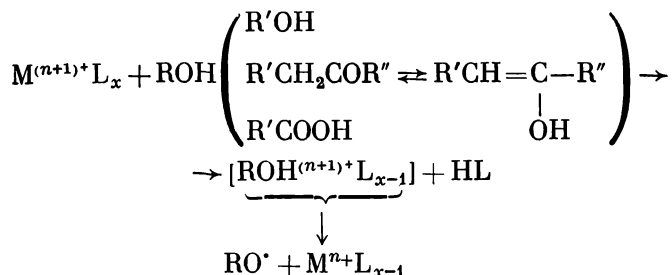
Participation of compounds of metals of variable valency in reactions of chain propagation and termination can be represented as follows:



It follows from the scheme that a two-stage regeneration of the catalyst takes place here (like in the case where the chains are generated).

The modern investigator has vast experimental material at his hand where the action of such catalysts in oxidation processes is described quantitatively. In order to calculate absolute magnitudes for rate constants of the interaction of peroxide radicals with compounds of metals of variable valency, wide use is made of chemoluminescence methods, the operating principles of which are based on the fact that only the process of radical re-combination gives luminescence in the course of the reaction.

We have so far only considered stages of the oxidation process that are not deep. At deeper stages, e.g. oxidation of hydrocarbons, formed are acids, alcohols, ketones, aldehydes, that can also react with the catalyst and be another source of free radicals, i.e. additional degenerate branching of chain will take place. The scheme of such branching is as this



All examples given in this chapter refer mainly to homogeneous catalytic reactions of oxidation. But investigations in heterogeneous catalysis of oxidation processes have now become very important from both practical and scientific standpoints. It appeared that the role of these processes is important not only in the gas phase, where the rate of diffusion of active particles is high enough compared with their life time (i.e. these particles, for example, radicals, can travel far from the point of their origination and take part in various reactions) but also in the liquid phase, where the diffusion rate is slow. Some modern aspects of heterogeneous catalysis of oxidation processes will be discussed in the next chapter.

## Chapter Fourteen

### Heterogeneous Catalysis

"The characteristic feature of the modern stage of investigations in heterogeneous catalysis is establishing the mechanism of the elementary stages and identifying intermediate surface compounds by the recently developed physical methods (for instance, EPR method, Mössbauer effect)."

*N. M. Emanuel, 1971*

Despite the great number of theories and hypotheses in the field of catalysis, many fundamental discoveries were unfortunately made by mere accident or as a result of a simple empirical approach. For example, the catalytic properties of mercury in the sulphonation of aromatic hydrocarbons were revealed by M. A. Ilyinsky when he accidentally broke a mercury thermometer over a reactor. Well known catalysts for Ziegler stereospecific polymerization, which have opened a new era in the polymerization process, were also discovered by a lucky chance.

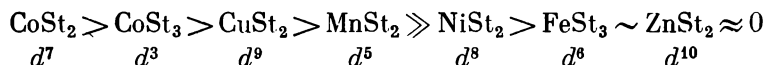
It is quite natural that this way of development of the science of catalysis cannot satisfy the modern demands. This explains the special interest in the study of the elementary stages of processes in heterogeneous catalysis. These investigations are the prelude to constructing scientific foundations upon which the scientists can rely in their quest of highly efficient catalysts.

Thus, direct experiments in EPR helped discover ion-radicals of oxygen on the surface of some oxidic catalysts containing e.g. ions of vanadium or molybdenum, which are selective catalysts for the gas phase oxidation of hydrocarbons.

The role of the heterogeneous catalyst in oxidation processes is very often to adsorb an organic compound and oxygen on its surface with formation of an adsorbed complex of these substances. Such a complex weakens the bonds of the components and makes them more reactive. In some cases a catalyst adsorbs only one component which dissociates into radicals. For example, propylene dissociates on cuprous

oxide to form an allyl radical  $\text{CH}_2=\text{CH}-\dot{\text{C}}\text{H}_2$  which readily reacts with oxygen.

It has become clear that the catalytic activity of metals of variable valency depends largely on filling of  $d$ -orbitals in cations of metal oxides. The ability of a metal ion to form complexes directly depends on the energy of its stabilization owing to the ligand field effect on the magnitude of the energy of splitting of the  $3d$ -level. The maximum energy of stabilization corresponds to filling of the  $3d$ -shell with three and seven electrons. In fact, we practically observe the maximum activity in metal ions  $d^3$  and  $d^7$ . For example, during decomposition of cumene hydroperoxide in cumene solution, the maximum catalytic activity is produced by oxides whose metal ions have 3 and 7 electrons in their  $d$ -shells ( $\text{MnO}_2$  and  $\text{NiO}_3$ ). The catalytic activity of metal compounds in reactions of decomposition of many hydroperoxides decreases in the following series:

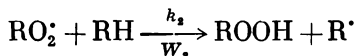


The rate of decomposition of hydroperoxides on various oxidic catalysts correlates with the rate of oxidation of the corresponding organic compounds. This positively indicates that the catalytic effect is in this case connected with the formation of additional quantities of free radicals in the process of oxidation at the expense of decomposition of hydroperoxides into radicals on the surface of the catalyst with subsequent transition of the free radicals into the mass of the oxidized substance.

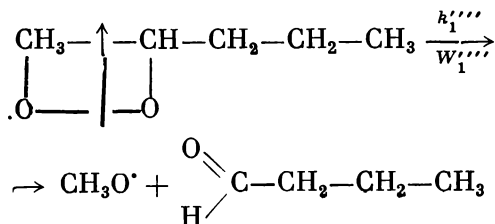
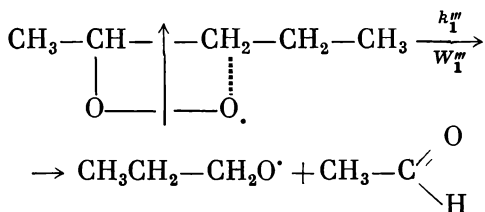
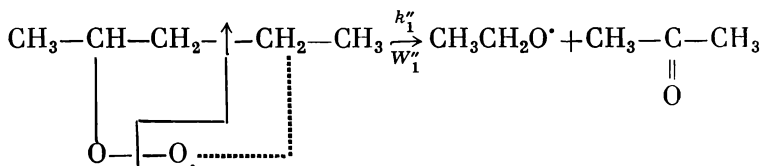
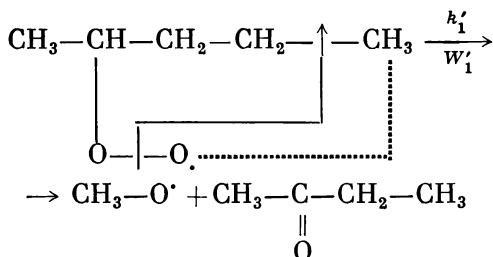
We have considered one of the possible ways of initiating the process, i.e. interaction of hydroperoxide with a catalyst. But in the case with oxidation, the reaction of heterogeneous initiation of chains can proceed either with decomposition of hydroperoxide into radicals, or with interaction of hydrocarbon and oxygen stimulated by the surface of a catalyst. Chains can be initiated by a charged form of an organic compound  $\text{RH}^+$  that is produced by the interaction of  $\text{RH}$  with the catalyst. Thus we have described the role of catalysis in the initiation (origination and branching) of chains.

The role of heterogeneous catalysts in reactions of chain propagation is especially evident from the change of the reaction rate and the direction of isomerization of peroxidic radicals.

It is known that during oxidation of organic compounds at sufficiently high temperatures, along with the bimolecular reaction of chain propagation



(in which hydroperoxide is formed without breakdown of the initial carbon skeleton of the molecule), we also observe isomerization and decomposition of peroxide radicals with the breakdown of the carbon skeleton and formation of a great number of various reaction products. For example, during oxidation of *n*-pentane, two parallel reactions occur:





It is quite apparent that the bimolecular way of chain propagation is selective since hydroperoxide is the only primary product (it readily converts into a small number of useful products). At the same time, monomolecular ways are not selective. They give many side products to decrease the yield of the main products (oxygen-containing oxidation products).

The rate of monomolecular isomerization and decomposition of peroxide radicals is:

$$W_1 = W'_1 + W''_1 + \dots + W_1^{(n)} = k_1 \text{RO}_2^{\cdot}$$

where  $k_1$  is the effective constant of the decomposition rate for peroxide radicals effected in various directions ( $k_1 = k'_1 + k''_1 + \dots + k_1^{(n)}$ ). The reaction rate of bimolecular chain propagation is:

$$W_2 = k_2 [\text{RO}_2^{\cdot}] [\text{RH}]$$

The ratio of the rates of monomolecular reactions characterizes selectivity of the process:

$$W_2/W_1 = \frac{k_2 [\text{RH}]}{k_1}$$

Catalytic inhibition of monomolecular chain propagation and activation of bimolecular reactions sharply improve selectivity of processes. This principle underlies the method of preparing acetic acid and methyl ethyl ketone by oxidizing *n*-butane in the liquid phase under conditions close to critical, and also the method for preparing propylene oxide by direct oxidation of propylene in solution in a reactor manufactured out of special material. (The reactor is made of titanium, which inhibits undesirable monomolecular processes and improves selectivity of the process.) Both methods have been proposed by N. M. Emanuel.

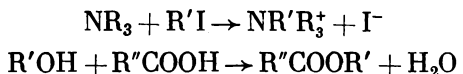
## Chapter Fifteen

### Reaction Medium Acts Like a Catalyst

"The modern state of the theory of solution cannot, except rare cases, establish definitely *a priori* on what the solvation of this or that substance in the liquid phase depends. The accepted division of solvation effects into 'specific' and 'non-specific' fails to disclose the essence of the problem but only states a well-known fact, viz., a dissolved particle can be affected both chemically and physically by the medium."

*S. G. Entelis, 1973*

We have already said that the role of a catalyst, from the point of view of energy, consists in lowering the energy barrier to be overcome by the reaction as a reacting system passes from the starting into the final state. The reaction medium, in which the particles under study are chemically converted, can in many cases perform this function. True, the effect of the medium on the course of the reaction in the gas phase is insignificant, but if the reaction occurs in a condensed medium, one should not disregard its catalytic effect on the kinetics of the chemical processes. N. A. Menshutkin was the first to notice the catalytic effect of the medium. In 1890 he studied the effect of the nature of the solvent on the rate of formation of tetrasubstituted ammonium salt from a tertiary amine and an alkyl halide, and also the rate of esterification reaction:



Menshutkin showed that the reaction of trimethylamine with ethyl iodide in nitrobenzene is 400 times faster than in hexane.

Interaction of solvent molecules (we shall discuss only liquid phase reactions) with the particles of the solute that undergoes a chemical conversion is known as solvation. The modern theory distinguishes two types of solvation, viz., non-specific (physical) and specific (chemical) solvation.

Non-specific solvation takes place in any solution and is due to the interaction of the solute with the field of the solvent molecules. In this case the medium acts on the reacting molecules like a continuum. Non-specific solvation is usually subdivided into non-polar and polar solvation. The former depends on the forces acting at short distances (dispersion forces, known also as the van der Waals forces or London forces). The latter depends on forces acting at long distances. They are of purely electrostatic nature (Coulomb forces). These interactions are very important only for molecules having a comparatively high dipole moment (the product of the charge and the distance separating the charges,  $\mu = el$ ). Specific solvation is effected by various types of coordination interaction, such as the formation of the hydrogen bond, of  $\pi$ -complexes, and other donor-acceptor complexes. These complexes are formed by partial transfer of one or two outer electrons from the donor to the acceptor.

In the general case, both the starting molecules and the end products, as well as the transition (activated) complexes of chemical reactions can undergo solvation. Solvation can both retard and accelerate the reaction. The transfer of an active particle from the ideal medium, where the interaction is absent, into a solvating medium liberates the energy of the interaction. The potential energy of the reacting system decreases as a result. If a transition complex of a chemical reaction is solvated stronger than the starting molecules, the energy of activation is lower than in the ideal medium, and the reaction rate increases. On the contrary, if the starting reacting molecules are solvated stronger, the activation energy increases and the reaction rate decreases. The character of the change in the energy barrier in these two cases is shown in Fig. 15.

In actual conditions, cases prevail where solvated are both the starting molecules and the transition states. The change in the reaction rate will therefore depend on the sign of the difference in the solvation effects of the starting reactants and the transition complex, provided any other complicating factors are absent. The solvation of the reaction products does not probably affect the rate of the process. Establishing in detail the mechanism of the solvation effects is one of the complicate problems in the study of the kinetic and catalytic manifestations of the effect that the

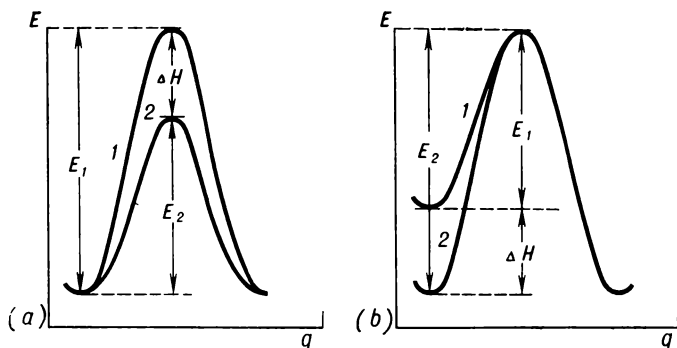


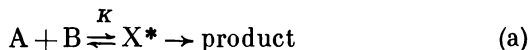
FIG. 15. Variation in the energy of the reacting system along the reaction coordinate during solvation of only activated complex (a) and only starting reactants (b).

reaction medium produces on chemical reactions. At the present time we have no substantiated quantitative theory that could 'universally' (using only one equation) describe the dependence of the reaction rate constant and the solvation equilibrium constant on the properties of the medium in which the reaction occurs. The situation is even more difficult because the change in the nature of the solvent can affect not only the kinetics of the reaction but its mechanism as well.

In order to describe quantitatively effects of positive and negative catalysis in the liquid phase reactions, the investigator would usually make use of the theory of absolute rates, the elements of which were described in Chapter Six. Less general but more understandable theoretical premises would be usually preferred. For example, in considering properties of solution (concentrated in particular), the investigator usually deals not with concentrations  $c$ , but with activity  $a$ , which relate as this:

$$a = \gamma c$$

where  $\gamma$  is an activity factor, found empirically, which is a measure of deviation of properties of a substance in solution from its properties in the state of the ideal gas. Bearing this in mind, consider a simple reaction of bimolecular interaction:



According to the theory of absolute rates of reactions, the rate equation has the following form:

$$V = \frac{kT}{h} [X^*] \quad (48)$$

where  $[X^*]$  is the concentration of the activated complex that can be expressed through the equilibrium constant of the transition process:

$$[X^*] = K^* [A] [B] \frac{\gamma_a \gamma_b}{\gamma^*} \quad (49)$$

where  $\gamma_a$ ,  $\gamma_b$ , and  $\gamma^*$  are activity factors of the starting reactants and the activated complex. Substituting Eq. (49) in Eq. (48) gives

$$V = \frac{kT}{h} K^* \frac{\gamma_a \gamma_b}{\gamma^*} [A] [B]$$

Whence the expression for the rate constant

$$k = \frac{kT}{h} K^* \frac{\gamma_a \gamma_b}{\gamma^*}$$

Activity factors of the reactants in the gas phase and of the activated complex can be assumed (without great error) to be unity, and the following known equation therefore holds for the specific rate constant of the reaction (a) in the gas phase:

$$k_0 = \frac{kT}{h} K^*$$

Comparison of the latter two equations shows that for quantitative assessment of the effect that the solvent produces on the reacting system, one should know the activity coefficients. To compare reaction rates in two different media, it is necessary to determine the activity coefficients of the reacting particles and the activated complex in these media:

$$k_1 : k_2 = \left( \frac{\gamma_a \gamma_b}{\gamma^*} \right)_1 : \left( \frac{\gamma_a \gamma_b}{\gamma^*} \right)_2 \quad (50)$$

But activity coefficients can be measured experimentally only for the starting substances A and B. Magnitudes for  $\gamma^*$  are calculated with the assumption that, with respect to its structure, the activated complex is similar to the starting compounds or the reaction products.

Within the limits of our concept of the activity coefficients the problem consists in finding the dependence of these coefficients on the properties of the medium. For example, if the reacting molecules are acted upon only by the dispersion forces, the following equation can be written for the rate constant of the bimolecular reaction (a):

$$RT \ln k = RT \ln k_0 + (V_a \Delta_a + V_b \Delta_b - V^* \Delta^*)$$

where  $V$  is the molar volume of the components A and B and of the activated complex, and the parameter  $\Delta$  is

$$\Delta = (P_1^{1/2} - P_2^{1/2})^2$$

where  $P_1$  and  $P_2$  are internal pressures of components in solution ( $P = E/V$ , where  $E$  is the energy of attraction between molecules of one sort). Since molar volumes do not, in the general case, change significantly with the change of the solvent, the rate constant is determined mainly by the difference between the internal pressures of the solvent and the reactants and the activated complex. If the internal pressure of the solvent is equal to the internal pressure of the reactants, but differs from the internal pressure of the activated complex, then

$$\sigma = (V_a \Delta_a + V_b \Delta_b - V^* \Delta^*)$$

will be a negative value and the reaction rate in this solution will be slower than in the absence of the solvent. The difference  $\sigma$  will be a positive magnitude and the reaction rate will be higher accordingly in that solvent whose internal pressure is equal to that of the activated complex but differs from the pressure of the reactants.

If dipole molecules take part in the reaction, the rate constant will depend on the dielectric constant of the medium  $\epsilon$ :

$$\ln k = \ln k_0 - \frac{1}{RT} \frac{\epsilon - 1}{2\epsilon + 1} \left( \frac{\mu_a^2}{r_a^3} + \frac{\mu_b^2}{r_b^3} - \frac{\mu_*^2}{r_*^3} \right)$$

where  $\mu$  and  $r$  are dipole moments and effective radii of the reacting particles and the activated complex respectively. This equation is known in the literature as the Kirkwood-Onsager equation. It is widely used to describe the dependence of the reaction rate on the polarity of the medium. In accordance with this equation, the rate constant can

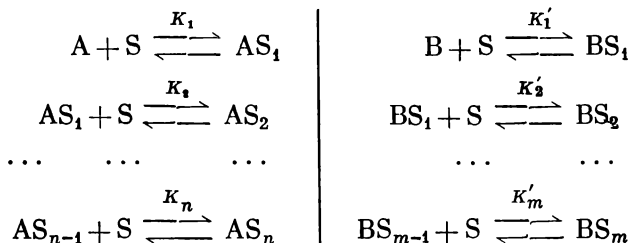
either increase or decrease, depending on the changes in the polarity of the medium and the sign of the expression

$$\sum \frac{\mu^2}{r^3} = \left( \frac{\mu_a^2}{r_a^3} + \frac{\mu_b^2}{r_b^3} - \frac{\mu_*^2}{r_*^3} \right)$$

If the dipole moment of the activated complex is equal to the sum of the dipole moments of the reacting particles, the dielectric constant of the medium does not produce any effect on the rate constant. If the value of  $\sum \frac{\mu^2}{r^3}$  is negative, the reaction rate increases with the polarity of the medium, and decreases if this value is positive.

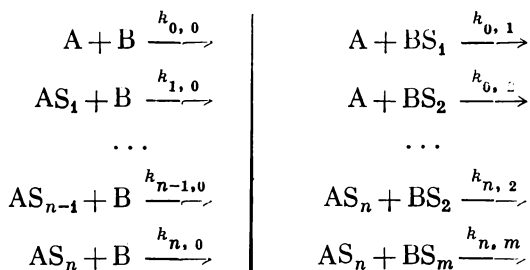
The validity of this equation has been tried in hundreds of various chemical reactions. It is amazing that despite many approximations that were admitted in deriving this equation, it quite satisfactorily describes many reactions. It should also be noted that the study of the dependence of the rate constant on the dielectric constant (to be more exact, the logarithm of the rate constant on the parameter  $(\epsilon - 1)/(2\epsilon + 1)$ ) makes it possible to assess the magnitude of the dipole moment of the transition state, i.e. to admit us into the realm of elementary chemical transformations.

The effect of specific solvation (complex formation) on the mechanism and kinetics of reactions can be described as follows. Adding complexing solvents into the reacting system quickly establishes equilibrium between non-solvated and solvated particles (molecules, ions, radicals). If we designate the reacting particles as A and B, the solvent molecules as S, and the number of solvent molecules coordinated with one particle A and B as  $n$  and  $m$  respectively, the following system of equilibrated reactions can be written in the general form



Along with these equilibria, the following reactions can occur in the reacting system, both solvated and non-solvated

particles taking part in these reactions



Once the dependence of the effective rate constant (that incorporates the rate constants of the elementary reactions and equilibrium constants of the complex formation process) on the concentration of the solvent in the system has been established, one can proceed to calculating absolute values of equilibrium and rate constants of the elementary acts. But it is very difficult to solve such a system of equations. Fortunately enough we usually deal with much simpler cases. As a rule, the coordination numbers  $n$  and  $m$  do not exceed 2. Usually only one of the reacting particles, A or B (rather than both of them) are solvated and this simplifies calculations.

In the most general case, the effect of the nature of the medium on the rate constant can be expressed by the equation

$$RT \ln k = RT \ln k_0 + RT \ln \left( \frac{\gamma_a \gamma_b}{\gamma^*} \right)_{\text{ns}} + RT \ln \left( \frac{\gamma_a \gamma_b}{\gamma^*} \right)_{\text{ss}}$$

where ns and ss refer to the terms responsible for non-specific and specific solvation respectively. In order to make practical use of this equation, it is necessary to express the activity coefficients of the reactants and the activated complex as functions of various types of specific solvation.



## Chapter Sixteen

### Catalysis in Biology

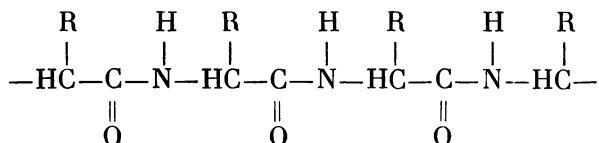
"Now... we encroach upon one of the main problems of experimental and theoretical investigation:

—what should we look for,  
—in what way should we look for this,  
—how should we learn, that we found what we have been looking for?"

*R. Bellman, 1961*

When you have read this chapter to the end, you will agree with the wise Bellman's words. True they were said on a different occasion but nevertheless the words hold for biological, or enzymatic, catalysis as well.

Enzymatic catalysis is closely connected with the vital activities of plant and animal tissues. Many (accounting to ten thousand) important chemical reactions occurring in a living cell are governed by special organic catalysts known as enzymes. The word 'special' should not puzzle the reader since we already know the material of which the enzyme is made. Nature has chosen only one building material, amino acids, and combined them into polypeptide chains of various length and composition:


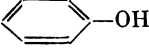
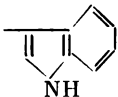


This is the primary structure of the enzyme, where R stands for lateral residues or most important functional groups of proteins, possibly posing as active centres of the enzymes. The structure of these residues, and also the corresponding amino acids and the values of  $pK_a$  for functional groups are given in Table 4.

These lateral groups accept the main load during the work of the enzyme, whereas the peptide chain functions as the skeleton. According to the Pauling-Corey model, the

Table 4

## Functional Groups of Amino Acids

Group	Amino acid	pK <sub>a</sub>
—CH <sub>2</sub> COOH	Asparagic acid	3.9
—(CH <sub>2</sub> ) <sub>2</sub> COOH	Glutamic acid	4.1
—CH <sub>2</sub> OH	Serine	—
—CH <sub>2</sub> 	Histidine	6.5
—CH <sub>2</sub> —  —OH	Tyrosine	10.1
—CH <sub>2</sub> —SH	Cysteine	10.3
—(CH <sub>2</sub> ) <sub>4</sub> NH <sub>2</sub>	Lysine	10.5
	Tryptophan	—
—(CH <sub>2</sub> ) <sub>3</sub> NH—C(=NH)—NH <sub>2</sub>	Arginine	12.5

structure is wound into a spiral stabilized in normal state by the hydrogen bonds between the acid and base centres:



There are enzymes consisting of pure protein (for example, urease, trypsin, chymotrypsin, pepsin) and also enzymes containing non-protein fragments, known as co-enzymes (e.g. carboxylase, catalase, cytochromoxidase). Thus, sometimes only special protein molecules can ensure normal work of the enzyme, whereas in other cases it is necessary to add some other components, e.g. a metal ion. However, it is not any protein that can act like an enzyme. For example, collagen or keratin are not enzymes.

The amino-acid composition, the arrangement of the acids in the chain, and also their complex spatial structure have been established for some enzymes. Nevertheless, this often fails to help us answer the main two questions: (1) why are enzymes so much selective and accelerate chemical conversion of molecules having only certain structure (which we have established as well), (2) how does the enzyme

lower the energy barrier, i.e. selects the most advantageous way (from the point of view of energy), owing to which reactions can proceed at normal temperature.

The high selectivity and rate of reaction are the main two characteristics of the enzymatic catalysis that distinguish it from laboratory and industrial catalysis. Not a single man-made catalyst (except, maybe, 2-hydroxypyridine) can rival the enzymes with respect to the effectiveness and selectivity of their action on organic molecules.

The activity of an enzyme, like of any other catalyst, also depends on temperature. The rate of enzymatic reactions increases with temperature. It should be noted that the activation energy  $E$  sharply decreases compared with non-catalyzed reactions. True, this does not hold universally. Many cases are known where the rate increases because of the increasing pre-exponential factor (that does not depend on temperature) in the Arrhenius equation.

Let us consider two examples illustrating the extraordinary efficiency of enzymes and compare their action with that of a common acid catalyst ( $\text{H}_3\text{O}^+$ ). All three parameters in the Arrhenius equation, viz., the rate constant ( $k$ , lit/mole·sec), pre-exponential factor  $A$ , and the activation energy ( $E$ , kcal/mole) will be used as the measure of activity.

Hydrolysis of urea:

$$\text{H}_3\text{O}^+ \quad k = 7.4 \times 10^{-7}, \quad A = 1.8 \times 10^{10}, \quad E = 24.6 \text{ (62 }^\circ\text{C)}$$

$$\text{Urease } k = 5.0 \times 10^6, \quad A = 1.7 \times 10^{13}, \quad E = 6.8 \text{ (21 }^\circ\text{C)}$$

Hydrolysis of adenosine triphosphate (ATP):

$$\text{H}_3\text{O}^+ \quad k = 4.7 \times 10^{-6}, \quad A = 2.35 \times 10^9, \quad E = 21.2 \text{ (40 }^\circ\text{C)}$$

$$\text{Myosin } k = 8.2 \times 10^6, \quad A = 1.64 \times 10^{22}, \quad E = 21.1 \text{ (25 }^\circ\text{C)}$$

These examples are especially interesting. The rate constant increases in the presence of urease mainly because the activation energy decreases (by 17-18 kcal/mole), whereas myosin affects the rate constant via the increasing pre-exponential factor, i.e. via the increasing entropy of activation. The main result is that the rate of the reaction increases thirteen orders.

The enzyme activity also depends on the acidity of the medium in which the reaction occurs. It is interesting to note that the curve describing this dependence resembles the bell-shaped curves of the acid-base catalysis (see above).

The pH range within which the enzyme shows its maximum activity is different for various enzymes (Table 5). The

Table 5

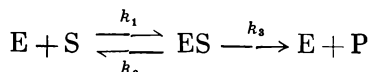
**Optimum pH at Which Enzymes Show Their Maximum Catalytic Activity Towards Substrate**

Enzyme	Substrate	Optimum pH
Pepsin	Egg protein	1.5
Pepsin	Casein	1.8
Pepsin	Hemoglobin	2.2
Acid phosphatase of blood	Glycerol phosphate	4.5-5.0
Amylase (malt)	Starch	5.2
Amylase (saliva)	Starch	6.8
Urease	Urea	6.4-6.9
Trypsin	Hemoglobin	8.0
Oxidase	Alanine	9.0
Succino-dehydrogenase	Succinate	9.0
Alkaline phosphatase of blood	Glycerol phosphate	9.5

study of this dependence is an important source of information on the nature of functional groups taking part in catalysis. Below we shall describe the methods by which this information is processed and to what conclusions it can lead us. But first we shall consider the kinetics of enzyme-catalyzed reactions. We already know that investigators meet with great difficulties in studying the mechanism of organic reactions by the kinetic methods. Even in the study of simple reactions, the investigator has to resort to simplified models of the conjectured paths of the reactions. What difficulties will the investigator face when he deals with enzymatic catalysis in which protein molecules have immense dimensions? Strange as it may seem, the mathematical apparatus is quite simple here. It is as simple as the model scheme itself by which the rate of enzymatic reactions is calculated. It was first proposed by Michaelis and Menten in 1913 and since then it has not changed in principle. Its essence is as follows.

It is assumed that the molecules of substrate S interact with enzyme E to form an intermediate enzymatic substrate

complex ES. Then happens something that is quite a mystery to us but this 'something' converts the substrate molecule into the end product P and simultaneously regenerates the enzyme



Note that although the enzymatic reaction is reversible we do not use the symbol  $k_4$  to show the backward reaction; this would indicate the conversion of E and P into the intermediate complex. This means that we consider the case where the conversion of the complex ES into the product governs the kinetics of the reaction. In other words, in the course of the reaction, the concentration of ES remains almost constant, hence

$$d[ES]/dt = 0 \quad (51)$$

Using the law of mass action, make out the expression for the rate of change in the concentration of ES:

$$d[ES]/dt = k_1[E][S] - k_2[ES] - k_3[ES] \quad (52)$$

Take into consideration still another expression, the material balance for the enzyme:

$$[E]_0 = [E] + [ES] \quad (53)$$

[ES] can now be determined from Eqs. (52) and (53) and substituted in Eq. (51)

$$W = k_1 k_3 [E]_0 [S] / (k_2 + k_3 + k_1 [S]) \quad (54)$$

Use the method suggested by Michaelis: divide the numerator and denominator of Eq. (54) by  $k_1$

$$(k_2 + k_3)/k_1 = k_m \quad (55)$$

The expression for the rate will then be

$$W = k_3 [E]_0 [S] / (k_m + [S]) \quad (56)$$

It is easy to analyse the obtained equation. It is evident that at low concentration of the substrate S the reaction rate should linearly increase with [S], but then, with growing [S] the rate will retard and at significantly high values of [S] 'saturation' will be attained. The maximum possible rate (at certain given conditions) is  $W_{\max} = k_3 [E]_0$ . In

order to calculate the parameters of Eq. (56) using experimental data, let us consider it in the linear form, or take the reverse values:

$$1/W = k_m/W_{\max} [S] + 1/W_{\max}$$

Then, within the coordinates  $1/W - 1/[S]$ , we have the equation of a straight line that cuts off section  $b$  on the axis of ordinates and has the angular factor  $a = k_m/W_{\max}$ ; ( $b = 1/W_{\max}$ ). The Michaelis constant and the maximum reaction rate can be calculated from these two equations. The physical sense of the constant  $k_m$  is found from Eq. (55): provided the condition  $k_2 > k_3$  is fulfilled, then  $k_m = k_2/k_1 = 1/K_{\text{eq}}$ , where  $K_{\text{eq}}$  is the equilibrium constant of formation of the enzyme-substrate complex. Thus,  $k_m$  is the constant of dissociation of this complex into the starting components. It characterizes a degree of enzyme affinity for the given substrate, i.e. the higher  $k_m$ , the smaller is the affinity.

Once the constant  $K_{\text{eq}}$  is known the free energy can be calculated as well:

$$\Delta G = -RT \ln K_{\text{eq}}$$

and having measured  $K_{\text{eq}}$  at different temperatures, we can determine the enthalpy and entropy of formation of the intermediate enzyme-substrate complex using the known equation

$$\Delta G = \Delta H - T\Delta S$$

Thus the study of the kinetics reveals important thermodynamic and kinetic characteristics of the enzymatic process. It is useful to consider the effect of conjugation of two elementary processes (formation and decomposition of ES) on the energy of the enzymatic reaction. If  $[S] < k_m$ , Eq. (56) is simplified to

$$W = k_3 [E]_0 [S]/k_m = k_3 K_{\text{eq}} [E]_0 [S]$$

whence we find the expression for the observed rate constant

$$k_{\text{obs}} = k_3 K_{\text{eq}} [E]_0$$

Taking the logarithm of this expression we have

$$\log k_{\text{obs}} = \log k_3 + \log K_{\text{eq}} + \log E_0 \quad (57)$$

Now remember that logarithms of the rate constant and the constant of equilibrium are expressed via the free energy of activation  $\Delta G_3^\ddagger$  and the free energy of the reversible reaction,  $\Delta G$ . Taking this into account, we can write for the two terms standing in the right-hand part of Eq. (57):

$$\Delta G_{\text{obs}}^\ddagger = \Delta G_3^\ddagger + \Delta G$$

Thus, the observed (effective) free energy of activation is the sum of the free energy of two conjugated stages of the enzymatic process, viz., the formation and decomposition of the intermediate complex. If the first (equilibrium or almost equilibrium) stage is favoured thermodynamically ( $\Delta G < 0$ ), this will decrease the observed free energy compared with  $\Delta G_3^\ddagger$ . As  $\Delta G$  increases in the direction of negative values,  $\Delta G_{\text{obs}}^\ddagger$  will decrease, i.e. the energy barrier of the reaction lowers and the reaction rate increases.

The experiment shows that the stage of formation of the complex ES is advantageous thermodynamically and is accompanied with the gain in free energy from 2 to 10 kcal/mole. Many separate components of the free energy  $\Delta G$  have been assessed quantitatively, and it turned out that the energy is gained at the expense of the enthalpy of formation of ES in some cases, and at the expense of the increasing entropy of the enzyme-substrate system in other cases. The latter fact indicates that during formation of ES the structure of the enzyme is loosened. The components ( $\Delta H$  and  $\Delta S$ ) of the free energy for various systems relate linearly. This indicates coordination of the elementary acts in the mechanism of formation of ES. An impression can be obtained that the enzymes are left to themselves to decide what is and what is not advantageous for them in each particular case: either to make a stronger bond between the active centre and the substrate molecule, or to bring its structure into the disordered state. For example, during hydrolysis of benzoyl-1-tyrosine amide with chymotrypsin, the formation of ES is accompanied with the gain in  $\Delta H = -10$  kcal/mole and the loss in the entropy  $\Delta S = -30$  cal/degree·mole. During the decomposition of carbobenzoxy-1-glutamyl-1-tyrosine with pepsin, the formation of ES is associated with the consumption of  $\Delta H = 3$  kcal/mole and the increase in the entropy to  $\Delta S = 24$  cal/degree·mole.

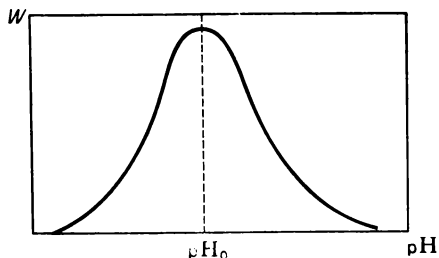


FIG. 16. Dependence of the observed rate of enzyme-catalyzed reaction on pH of the medium.

It is difficult to say what guides the enzyme in its choice of the method to activate the substrate, but, after all, the study of the kinetics of the enzymatic reaction and thermodynamics of the formation of the intermediate complexes (although it gives quantitative information) fails to disclose fully the molecular and electronic mechanism of the enzyme work. Like in the study of non-catalyzed reactions, we have to construct models, that is, to invent mechanisms that would not at least contradict the experimental data and the elementary logics of chemical reactions. The trouble is that with properly working imagination, one can 'invent' a host of 'good working' mechanisms. We shall acquaint you with some conjectured models later but now consider the methods by which the investigators establish the nature of active centres of enzymes.

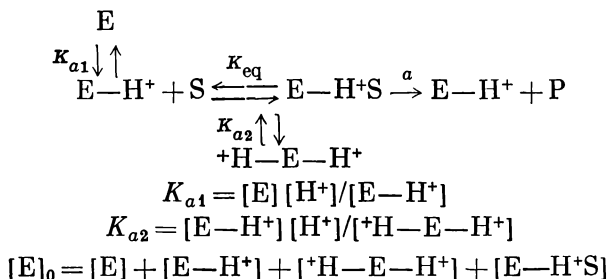
We have already said that the enzyme activity strongly depends on the acidity of the medium. A graph illustrating the dependence of the reaction rate on pH of the medium is a bell-shaped curve with the maximum at a certain value of pH (Fig. 16). How can this behaviour of enzymes be explained? One of the hypotheses connects it with processes of ionization of the enzyme active centres by the ions  $\text{H}_3\text{O}^+$  and  $\text{OH}^-$  of the aqueous medium. This is a very good idea. It fully agrees with the known (in organic chemistry) facts of sharply changing reactivity of functional groups in response to changes in their ionic state. We have seen that protonization of the amino group makes it inactive towards electrophilic centres of the other molecule, and protonization of the carbonyl oxygen, on the contrary, increases the reactivity of the carbonyl carbon towards nucleophilic



reagents. It can be assumed that something similar happens in the enzymatic catalysis with varying acidity of the medium. The increasing acidity will favour some elementary stages and will be unfavourable for the others. In the presence of such competing facts, one must guess the existence of a certain optimum acidity at which the enzyme activity is maximum. Let us try to describe this competition quantitatively.

Suppose that one of the active centres becomes active only when it is protonized. It is evident that the number of such protonized forms increases with the acidity, and hence the rate of the reaction increases as well. Now suppose that other active centres participating in the catalyzed reaction turn inactive under the effect of protonization. The proportion of such inactive sites will grow with acidity, and since the enzymatic catalysis occurs with simultaneous participation of both centres, the reaction rate must decrease. It is easy to guess that if the number of protonized centres of both types could increase in synchronism with acidity we would never observe any enzymatic catalysis because of mutual compensation of the activation and inactivation effects produced by the  $\text{H}_3\text{O}^+$  ion. In reality there is no such equality in the proton-accepting properties of active centres, and this gives the bell-shaped dependence of the reaction rate on the pH of the medium. The affinity of the active centre for proton can be expressed by the dissociation constant  $K_a$ . (Remember that the negative logarithm of  $K_a$  is designated as  $\text{p}K_a$ , and the greater this value, the higher is the activity of a given centre.) Thus, two dissociation constants,  $K_{a1}$  and  $K_{a2}$  should be used to describe the work of two active centres.

Now let us make out a kinetic scheme of catalysis that would account for the protonization effects of active centres:



The scheme is rather self-explaining. We shall give only the result of calculations, the formula expressing the dependence of the reaction rate on the hydrogen ion concentration

$$W = \frac{aK_{eq}K_{a2}[E]_0[S]}{[H^+]^2 + (K_{a1} + K_{a2})[H^+] + K_{a1}K_{a2}} \quad (58)$$

If a reader wants to know how we derived this formula, he can process the above equations. He should only remember that the idea of a stationary reaction underlies the calculations. It is based on the assumption that the concentration of the transition complex does not significantly change in the course of the reaction and the derivative of  $[EH^+S]$  (time) is therefore zero. To obtain an expression for the optimum hydrogen ion concentration (optimum pH) one should differentiate Eq. (58) with respect to  $[H^+]$  and equate the obtained result with zero. Then we have

$$[H^+]_{opt}^2 = K_{a1}K_{a2}$$

whence

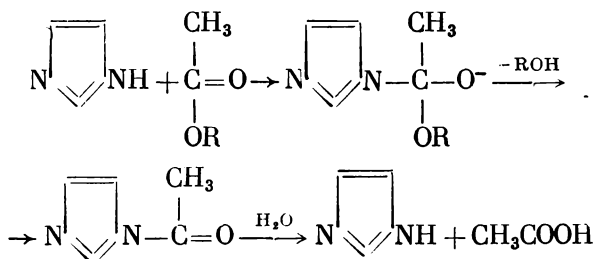
$$pH_{opt} = 0.5(pK_{a1} + pK_{a2})$$

Thus the optimum pH for this simple case at which the rate of the enzymatic reaction is maximum is half-sum the basicity indices  $pK_{a1}$  and  $pK_{a2}$  of active centres participating in the reaction acts of catalysis. Once the value of optimum  $pH_{opt}$  and one of the  $pK_a$  values are known from experiment, the other constant can be determined as well. (There are special kinetic methods that can be used to assess separately  $pK_{a1}$  and  $pK_{a2}$  but we shall not discuss them.) For example, in the study of the pH-dependence of starch hydrolysis to maltase by the action of  $\beta$ -amylase, it has been established that two active centres, having  $pK_a$  4.3 and 7.1, take part in the catalysis. Table 5 shows that these centres can be, for example, carboxylic group of asparagic acid and the imidazole ring of histidine. Active centres having the  $pK_a$  6.2 and 7.7 take part in the hydrolysis of acetylcholine in the presence of cholinesterase and centres having the  $pK_a$  of 6.6 and 9.0 take part in the urease decomposition of urea, etc.

So the analysis of the reaction rate dependence on the pH of the medium is an effective means to identify functional groups of the protein molecule of an enzyme that take part in the activation of the substrate molecules. If we know the

nature of active centres, we can imagine how they work. True, we have to apply the same mechanisms of the elementary acts that we use in the study of non-catalyzed reactions in organic chemistry. It is unnecessary to use any special mechanical concepts. There is a conviction that the work of an enzyme consists, after all, in the arithmetic sum of simple operations like those occurring in the interaction of organic molecules in usual laboratory test-tube conditions.

Let us consider the mechanism of esters hydrolysis by chymotrypsin. Remember that the study of the dependence of the hydrolysis rate on the pH of the medium in the presence of chymotrypsin has shown that the maximum on the curve illustrating this dependence is at pH of about 7. This value corresponds approximately to the value of  $pK_a$  of the imidazole fragment of histidine. This single fact gave grounds for a suggestion that nitrogen atoms of the imidazole ring took part in the activation of the ester molecule. In fact, model experiments with catalyzing similar hydrolytic reactions with imidazole and its derivatives have shown that the latter produce accelerating action. The mechanism of the model reactions comprises the formation of a transition product of addition of ester to the nitrogen of the imidazole ring, for example:



It seems that this information proves that chymotrypsin 'works' by the same principle. But in reality it turns out that the enzyme-substrate complex (ester + chymotrypsin) is a product of interaction of the ester group with the hydroxyl group of the serine residue (*O*-acylserine). It also turns out that the straight chain of amino acids that are part of the active site of chymotrypsin, Gly—Asp—Ser—Gly—Pro—Leu, does not contain histidine residue in the vicinity of serine. It remains to suggest that the active centres of chymotrypsin, the hydroxyl group of serine, and the imida-

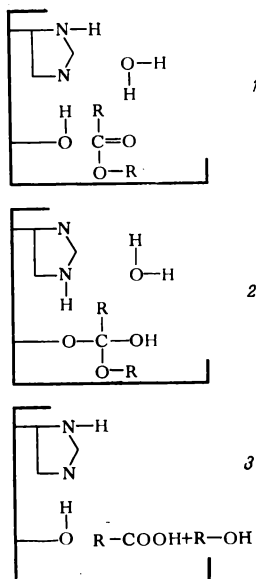


FIG. 17. Probable mechanism of hydrolysis of an ester by chymotrypsin with participation of two functional groups of the enzyme, namely the imidazole ring of histidine residue and the hydroxyl group of serine residue. 1, 2, and 3 designate the stages of the process. A solid line shows conventionally the polypeptide chain to which the active sites of the enzyme are attached.

zole ring of histidine, although separated from one another (e.g. they are located at different coils of the polypeptide chain in the Pauling-Corey model), can approach each other just at the moment when a molecule of the ester is captured by one of the active centres of chymotrypsin.

What are the details of the mechanism of this 'approach' and what is the motive force of this 'mechanochemical' process? No one can so far answer these questions with full certainty. The hypothesis of D. Koshland concerning induced correlation admits that the motive force is the substrate molecule itself that organizes the active centres into favourable geometrical (spatial) arrangement with respect to the reacting centres of the substrate. One of the conjectured mechanisms of the enzymatic hydrolysis of an ester is shown in Fig. 17.

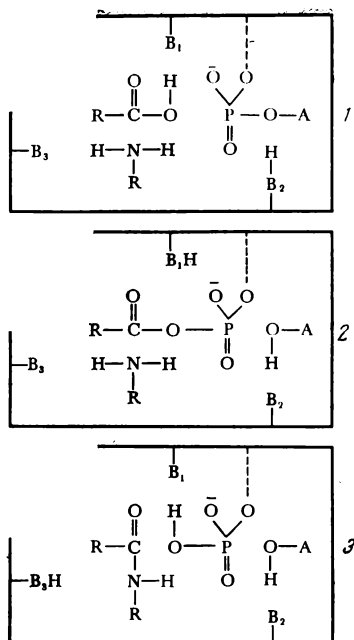


FIG. 18. Proposed three-step scheme of the mechanism of synthesis of the peptide bond during the reaction of the amino group with the carboxyl group inside the enzyme.  $B_1$ ,  $B_2$ , and  $B_3$  are active sites of the enzyme (synthetase) acting mainly as acceptors and donors of protons.

Another example is the mechanism of synthesis of the peptide bond by an enzyme, whose nature is not important for the time being. The process begins with the capture (from the aqueous medium) of molecules of carboxylic acid  $R_1COOH$  and amine  $R_2NH_2$  that adhere to certain sites of the enzyme. The latter must then ensure the encounter of the participants of the reaction and this encounter must ensure direct contact of their active centres. If the sites of adherence are too far from one another (and this perhaps is actually so), the required contact can only be effected by coiling the protein molecule. Consider the process from the moment when the polypeptide chain of the enzyme molecule coils properly and the short-distance force of the chemical interaction becomes effective (Fig. 18).

Suppose that all begins with the attack by the hydroxyl group on the phosphorus atom of ATP, that results in the formation of the first intermediate product, acyl phosphate. This is a very unstable reactive product. The diagram shows that this act is promoted by the rupture of the oxygen-phosphorus bonds and the participation of the acid proton in the hydrogen bond with a certain functional group  $B_1$ . Now suppose that the chain bearing the molecules attached to it has coiled up so that the amine molecule is in the vicinity of acyl phosphate. But this is not the mere fact of being in the vicinity that matters, but rather a certain orientation of the amino group nitrogen and of the carbonyl carbon. If the atoms are oriented as shown in Fig. 18, the known nucleophilic attack by nitrogen on the carbonyl carbon will give the nitrogen-carbon bond with simultaneous rupture of the carbon-oxygen bond. The amino acid molecule is then desorbed from the enzyme surface, the eliminated phosphate group is attached to diphosphate to form the starting ATP, and the enzyme molecule becomes prepared to repeat the process with new molecules of the acid and amine. The acts (the substrate capture, chain coiling up, series of elementary acts connected with the rupture of the old and formation of new bonds, desorption of the product, regeneration of catalytic centres, and uncoiling of the chain) are repeated until something unexpected happens in one of the links of this mechanism.

It follows that the elementary chemical acts occur within the boundaries of space commensurable (the order of magnitude) with the dimensions of the reacting groups and bonds. But why are the enzymes so large? Is it the result of the imperative necessity (to increase the selectivity) or of a random selection in the evolution of the living nature? Modern science cannot now answer this question. It has been, for example, established that the removal of a large portion of the protein molecules of myosin and papain does not significantly change their enzymatic activity. It means that the catalytic function of the enzyme can be realized not only with the whole protein molecule but also with part of it. A new question arises, why did nature construct complicate catalytic molecules and did not limit itself to a more reasonable (from our point of view) method of using that number of amino acid residues that is necessary for normal biochemical functioning? The scientists abstain

from comments on this problem too. We only know that when the enzyme is fully split into amino-acid residues, it fully loses its properties since these residues do not show any catalytic activity in reactions where the whole polypeptide chain would otherwise accelerate the process.

When we discuss the mechanism of enzymatic reactions, we make some assumptions but the operating principle of the enzyme action is probably understood correctly. Does it unveil some intimate sides of the problem, and can we believe that our modern views on catalysis are close to reality? Let us assume for a minute that everything happens just like we think it does (see Figs. 17 and 18). Which of the links in the chain of events looks the least clear? Since we know (though in general outline only) how the elementary chemical acts are realized, we can extend these concepts to chemical acts occurring in the reaction space of a coiled enzyme. After all they can be described as probability of rearrangement of chemical bonds. And if all functional groups taking part in the process are known, everything can, in principle, be calculated and taken into account. What we still do not know is how the reaction volume is formed with its amazing ability to orient the active centres of molecules in *only this and no other way*. But even this can be perceived if we resort to analogy.

In Chapter Nine we discussed mutarotation of monosaccharides and considered one of the stages at which the pyranose ring closed. The Dreyding model helps understand it. It shows that whatever we do with the monosaccharide chain, it will sooner or later arrange itself so that the hydroxyl group at  $C_5$  becomes oriented exactly to oppose the glycoside centre. (All other substitutes at other carbon atoms are oriented so as they were in the starting cyclic molecule, i.e. *only in this and no other way*. But if, with the appropriate orientation, the active centres possess certain affinity for one another, the chain will inevitably close. The main point in this example is the strict orientation of active centres, which is sooner or later attained in conditions that seem to be a chaotic motion of separate chain fragments. And there is nothing mysterious in it. We know how it all happens. All interatomic distances have quite definite values, the atoms and functional groups are arranged at carbon atoms in strictly definite positions, and therefore, whatever movements the chain fragments perform about

the carbon-carbon bonds, the active centres will at last rest in quite fixed positions. Everything therefore depends on the strict organization of molecular structures, on the order in which atoms are bonded and on their spatial arrangement with respect to the centres to which they are attached.

Does it mean that we know how the peptide chains of the enzyme protein molecule coil to ensure the strict orientation of active and reaction centres? Generally speaking, yes, since after all we can construct a mechanical model and see how it must be twisted (without destroying the chemical bonds and valency angles, but only rotating separate fragments relative to one another) so that these centres are brought together to a certain critical distance.

To summarize, we know the following: (1) at least two functional groups take part in the enzymatic catalysis and the mechanism of the enzyme-catalyzed reaction is a certain succession of elementary acts that guide the reaction along a more advantageous pathway compared with a non-catalyzed reaction; (2) active centres on the polypeptide chain are so arranged that, at a certain moment of time and at a certain site, they can interact with the substrate molecule and realize a series of coordinated chemical acts.

So what is it that we do not know about the nature of the enzymatic catalysis? It is just time to remember the beginning of the chapter and the cited Bellman's words. In fact we do not know *what* we still have to find out about this phenomenon, and we do not know *how* we shall learn some day that we have found the *very thing* we were looking for. If with all our knowledge of the enzyme structure and its work we could construct a system, in all respects similar to an enzyme, then we might feel sure that we understand this phenomenon. And in our opinion, this is just *what* we need.





